federal register

FRIDAY, JANUARY 6, 1978

PART II

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

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OTC TOPICAL ANTIMICROBIAL PRODUCTS

Over-the-Counter Drugs Generally Recognized as Safe, Effective and Not Misbranded

[4110–03]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 333]

[Docket No. 75N–0183]

OVER-THE-COUNTER DRUGS GENERALLY RECOGNIZED AS SAFE, EFFECTIVE AND NOT MISBRANDED

OTC Topical Antimicrobial Products

AGENCY: Food and Drug Administration.

ACTION: Tentative Final Order.

SUMMARY: This tentative final monograph would establish conditions for the safety, effectiveness, and labeling of over-the-counter (OTC) products such as antibacterial soaps, surgical scrubs, skin cleansers and first-aid preparations. The monograph is based on the recommendations and findings of the OTC Antimicrobial I Panel and a proposal by the Commissioner of Food and Drugs, in accordance with procedures for the agency's ongoing review of OTC drug products.

DATE: Objections and/or requests for oral hearing before the Commissioner by February 6, 1978.

ADDRESS: Written objections and/or requests for hearing to the Hearing Clerk (HFC–20), Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20857.

FOR FURTHER INFORMATION CONTACT:

William E. Gilbertson, Bureau of Drugs (HFD–510), Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20857, 301–443–4960.

SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of September 13, 1974 (39 FR 33103), the Commissioner issued a proposal, pursuant to the OTC drug review procedures in § 330.10 (a)(6) (21 CFR 330.10(a)(6)), to establish a monograph for OTC topical antimicrobial products for repeated daily human use, together with the report of the OTC Antimicrobial I Panel, which is the advisory review panel responsible for evaluating data on drugs in that category. Interested persons were invited to submit comments on the proposal within 60 days—on or before November 12, 1974. Reply comments in response to comments filed during the initial 60-day period were allowed until December 12, 1974.

The Commissioner advises that some of the labeling terminology proposed in this document, especially those terms relating to indications and directions for use, may not yet be fully informative to some persons. The Commissioner invites further public comment on the present content and format of the labeling required in the tentative final monograph so that all interested persons may have an opportunity to submit their views and the agency has the benefit of as broad a spectrum of opinion as possible on this aspect of the proposal.

All comments and the proposed labeling will be carefully evaluated, and any changes deemed necessary will, if appropriate, be made in the final monograph.

Numerous comments requested extension of the deadlines for comments and reply comments because of the complexity of the Panel report and proposed monograph and because the information evaluated by the Panel would not, in accordance with § 330.10(a)(2) of the OTC drug review procedures, be available until 30 days after publication. The Commissioner granted the request and issued a notice in the FEDERAL REGISTER of October 3, 1974 (39 FR 35675) granting a 30-day extension of the deadline for comments until December 15, 1974, and the reply comment period was extended until January 1, 1975. The data and information considered by the Advisory Review Panel were put on public display 30 days after publication, i.e., on October 13, 1974, in the office of the Hearing Clerk, Food and Drug Administration, after deletion of a small amount of trade secret information.

In response to the proposal, 86 comments and reply comments were received from 16 trade associations, 45 drug manufacturers, 1 consumer group, 24 consumers, and 4 professional or scientific associations.

The Commissioner has reviewed the report and proposed monograph and all the comments and reply comments. The Commissioner has decided, for clarity, to divide his conclusions in this document in the following sections:

1. The Commissioner's conclusions on the comments and reply comments.

2. The Commissioner's restatement of the Panel's recommendations and conclusions for Category II (not generally recognized as safe and effective or would result in misbranding) and Category III (available data insufficient for classification) and the Category III testing guidelines. The Commissioner will adopt these findings by restating the appropriate sections of the Panel's report in this document, with modifications for clarity and regulatory accuracy, and by accounting for new data or information that has come from this rulemaking proceeding. Extraneous or unsupported statements will be excluded. If the Commissioner agrees with a comment that suggests a modification of the Panel findings, he will incorporate appropriate changes in the restated version of these sections.

3. The Commissioner's conclusions and tentative final monograph. All of the Commissioner's decisions regarding the Panel's recommendations and conclusions for Category I conditions (generally recognized as safe and effective), including his modifications justified by the comments, will appear in the tentative final monograph. The Commissioner advises that for purposes of clarity the format of the labeling section of the tentative final monograph has been revised from that originally contained in the proposed monograph.

The Commissioner has carefully considered the environmental effects of the proposed regulation and, because the proposed action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. A copy of the environmental impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

I. THE COMMISSIONER'S CONCLUSIONS ON THE COMMENTS AND REPLY COMMENTS

A. GENERAL COMMENTS

1. Several comments contended that the agency does not have the authority under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.) to establish substantive rules other than by formal rule making.

This subject was dealt with in detail in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drugs, published in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464, 9471–9472), and the Commissioner reaffirms the conclusions stated there.

2. One comment contended that the Commissioner's preamble statement relating to the question of whether long-term use of antimicrobial bar soaps alters the normal balance of organisms on the body (published in the FEDERAL REGISTER of September 13, 1974 (39 FR 33103)) is a "disclaimer that contravenes paragraph 74 of the May 11, 1972, preamble to the procedures for classification of OTC drugs (37 FR 9470), which rejected as unnecessary a suggestion that the OTC drug procedures specifically state that the Commissioner is not bound by a Panel's monograph.

The cited paragraph, which stated the Commissioner's conclusion that a boilerplate explanation of the function of an advisory committee need not be included in the OTC drug procedures, cannot sensibly be read as a prohibition on the Commissioner's right to comment on a Panel report, to explain or highlight a particular problem, or to emphasize that controversial Panel decisions are subject to additional public procedure and do not represent the final judgment of the agency. The Commissioner will identify areas of controversy or doubt in future Panel reports when, in his judgment, to do so will stimulate maximum public response to these documents.

That long-term use of antimicrobial soaps may alter the normal balance of gram-positive and gram-negative organisms on the body was plainly characterized by the OTC Antimicrobial I Panel's report as a hypothesis, not a proven fact. However, the contrary impression may have been created by the emphasis that the news media gave this one section of the report. The Commissioner therefore included a statement in the preamble designed to bring the matter into perspective and encourage debate on the scientific merits of both sides.

3. One comment stated that "the Panel's duty was to evaluate antimicrobial ingredients, but it made recommendations clearly extending to nonantimicrobial ingredients." The comment

claimed that such recommendations exceed the legal boundaries of the Panel's responsibility. The comment requested that "the Commissioner modify the monograph to make it clear that its effect is limited to products with antimicrobial ingredients."

Some products that have been traditionally considered first-aid for minor skin wounds are also designed to protect against infection, either by chemical or physical means. These products contain ingredients intended to exclude contamination by microbes, together with antimicrobial ingredients to inhibit the growth of the microbes. These differing functions are interdependent and logically can be considered together as part of a total system aimed at excluding harmful microorganisms from wounds in the human body. The Commissioner believes that consideration of all the ingredients in such a system is within the charge of the Antimicrobial I Panel.

4. Several comments objected to the degree of testing recommended by the Panel. They argued that such testing was unnecessary and a waste of time, resources, and money. This conclusion was predicated on the belief that ingredients listed in Category III have been used safely and effectively for many years. The comments called upon FDA to issue a financial impact statement. The costs of such testing would exceed the sales of some products, it was contended, and, according to one comment, such products would be withdrawn from the market in spite of past successful marketing. The comment suggested that the cost of required testing be underwritten by the government rather than by manufacturers.

In performing the task it was assigned, the Panel used its best judgment about what testing requirements are required for ingredients placed in Category III. The OTC drug review regulations and the historical evidence negate the generality that longtime use of an OTC product without obvious toxic consequences, or with apparently beneficial results based on clinical observation, constitutes, in and of itself, the kind of proof of safety and effectiveness that is demanded by current scientific standards.

The Commissioner does not intend to create testing regimens more burdensome than needed to prove safety and effectiveness, as required by the law. The fact that testing must be scientifically valid and adequate to reach reliable conclusions, and therefore may be costly, is a product of the statutory standard as applied by experts to the principles of drug investigation. The Commissioner does not believe that such testing will place undue burdens on the industry and the research community. Although the cost of testing a product to meet FDA regulations may in exceptional cases exceed the sales of a product in any given year, it is improbable that such cost would exceed sales over a significant fraction of the market life of a product. The financial impact statement requested by these comments is on file in the office of the Hearing Clerk, Food and Drug Administration.

The Commissioner is alert to the need to conduct scientifically valid tests in an economical manner and without unnecessary duplication of effort. However, the public must be assured that marketing of products with Category III ingredients or claims is permitted only on condition that appropriate testing is concurrently carried out to resolve questions that have been identified by the Panel concerning safety and effectiveness. Testing requirements for Category III have been established with these considerations in view.

5. One comment requested "that those employees who served the Panel in an official capacity not take an active role in the preparation of the tentative final regulation."

There is no statutory requirement for separation of functions in rule making proceedings. The Commissioner, however, in the exercise of his discretion, does require in 21CFR Part 10 a separation of functions with respect to any matter subject by statute to an opportunity for a formal evidentiary public hearing and to any matter subject to a public hearing before a Public Board of Inquiry. He is not prepared at this time to consider extending the separation of functions beyond these matters. He believes, moreover, that it would be disruptive to require separation functions at this late date in the OTC drug review, that it is unnecessary in view of the essentially nonadversarial character of the review, and that it would be wasteful given the limited staff resources of the agency. It is imperative that those with the greatest expertise be used both to assist the Panel and to participate in preparing the tentative final and final monographs. Employees who have worked with the Panel best understand its reasoning and deliberations. They are therefore best qualified to review comments on the Panel's report. Of course, the comments on the proposed monograph are reviewed not just by those individuals who served on the Panel, but by many others in the agency. Consequently, the views of those persons who assisted the Panel will not prevail unless they are scientifically reasonable and sustainable on the record.

6. Several comments stated that FDA "bears the burden of proving the statutory solution" with respect to OTC drug regulations, and that the "agency must demonstrate by a preponderance of the evidence that a drug is not generally recognized as safe and effective."

It is not clear what was intended by these statements. If the comments mean that the agency must establish a basis and purpose for the regulations it issues, they are correct. Section 4 of the Administrative Procedure Act (5 U.S.C. § 553) requires that the agency incorporate in each regulation a concise general statement of its basis and purpose. As noted above (paragraph I.A.1.), the legal status of OTC drug monographs is discussed elsewhere.

7. A comment stated that "If each and every company must submit active ingredients, vehicle and total product tests recommended by the Panel this would be tantamount to a pre-clearance requirement on every product. It is our understanding that FDA chose the OTC Drug Review route to avoid this."

The Commissioner will not require every company to test and will ordinarily not require testing of the active ingredient, vehicle, and total product. However, within the broad and varied field of OTC drugs there may possibly be circumstances in which review and testing of individual products is the only way to determine whether the statutory and regulatory criteria are met. While this may result in more extensive testing for a very few classes of OTC products than was envisioned at the beginning of the OTC drug review, the requirements applicable to those products will be nowhere near as extensive and detailed as the new drug application (NDA) requirements. For certain product classes in this monograph, where issues of skin sensitivity and irritation are of importance, data will have to be submitted on active ingredients, vehicles, and/or total products. Those ingredients or product classes will be delineated in appropriate testing guidelines.

8. A comment claimed that "there is no provision in the law for Category III." The gist of the comment is that Category III status is incompatible with continued lawful marketing of a product without an approved NDA.

This issue is currently the subject of litigation in the U.S. District Court for the District of Columbia, *Health Research Group* v. *Kennedy*, Civ. Action No. 77–0734. The Commissioner's position on the matter will be explained in that forum.

9. One comment suggested that all Category III products should bear the label statement "WARNING * * * the safety of this product has not been determined."

Products in Category III have been on the market for many years. Classification in this category permits them to remain on the market for a brief additional period while evidence is developed to permit their final classification into either Category I or Category II. A product may be in Category III for a number of reasons having nothing to do with safety, including questions about its effectiveness. To require all Category III products to bear a safety-related warning for a brief period of time while these questions are resolved would be misleading in many cases. The warning as phrased is, moveover, misleading even for products that have been placed in Category III to obtain more safety data. It implies a complete absence of information supportin gthe safety of products for which there will ordinarily be a lengthy history of safe use and a considerable body of expert opinion that they present no hazard. The Commissioner advises that drugs are not placed in Category III if currently available data raise serious concerns about their safety. Such drugs are either placed in Category II or sub-

jected to expedited regulatory action outside the OTC Drug Review procedures, depending on the reliability and conclusiveness of the data and the degree of harm the drug might cause.

10. Numerous comments objected to the 1-year limit for testing products with claims based on Category III ingredients, primarily because of the large number of products in Category III that require testing and the resulting bottlenecks in personnel and laboratory facilities that would make it impractical to carry out the required safety and stability tests within the 1-year period.

The Commissioner concludes that because of the extensive testing requirements and the many ingredients in Category III, a 2-year testing period would be appropriate. He therefore concludes that Category III conditions should be permitted to remain in use for 2 years after the date of publication of the final monograph in the FEDERAL REGISTER.

11. A comment contended that the Panel appears to have set standards contrary to the concept that OTC drugs are generally symptom-oriented, in contrast to prescription drugs, which are disease-oriented, and, therefore, that the Panel exceeded its charge.

The Panel was charged with judging the scientific merit of claims for safety and effectiveness of OTC products containing antimicrobial ingredients for topical human use, which include soaps, surgical scrubs, skin washes, skin cleansers and first-aid preparations, pursuant to § 330.10(a) (1). Those claims are made by manufacturers, repackers, and relabelers of OTC drugs, not be the agency. The Commissioner must judge the merit of these claims no matter what their specific nature. There need be no unanimity of opinion on whether a particular claim made for an OTC product is symptom- or disease-oriented. The merit of a claim for safety or effectiveness can be judged regardless of whether the claim deals with a disease- or symptom-oriented characteristic. The symptom or disease nature of a phenomenon is of scientific interest, but is not relevant to the Commissioner in judging whether or not the consumer is receiving what he is paying for in terms of a particular claim made for a product.

Although the Commissioner recognizes that OTC drugs are generally symptom-oriented rather than disease-oriented, he is aware of several areas in which OTC products are used to treat disease, e.g., athlete's foot and acne. Since the difference between symptom and disease is not well defined, each OTC drug ingredient claim will be judged on its own merit for safety and effectiveness regardless of whether the claim is directed to a disease condition or symptom.

12. A comment expressed concern over the Panel's recommendation that, if it were not possible to adequately control antimicrobial ingredients in cosmetics, "the Food and Drug Administration institute whatever action is necessary to reclassify cosmetic products containing antimicrobial agents as drugs," and stated that NDA's should be required only when drug claims are made.

The Commissioner does not intend at this time to require NDA's for products that contain a Category I antimicrobial ingredient at greater than preservative levels, but make no drug claim for such ingredient. Nor will Category III safety testing be required for cosmetics containing antimicrobial agents so classified. However, all drug ingredients now requiring safety or effectiveness testing will eventually be reclassified into either Category I or Category II. Any antimicrobial ingredient for drug use that is placed in Category II for safety reasons will, under separate regulations, be banned from use, or restricted to preservative level use, in cosmetics.

13. There was comment from authors of papers describing the use of antimicrobial soaps on patients isolated in hospital "life island" facilities. It was said that Panel statements about the papers do not clearly distinguish between the authors' and the Panel's opinions. The authors wished to make it clear that their work shows major reduction of bacterial-colony-forming units on all body sites tested, including reductions in gram-negative bacterial counts. The comment, further discussing bacterial reduction, stated that the bacteriostatic soap preparations used in these studies were "certainly equivalent to preparations containing hexachlorophene."

The Commissioner agrees that the language of the report should have made it clear that the Panel was stating its own analyses and conclusions rather than those of the authors of the cited scientific papers.

14. Comments criticized the composition of the Panel, which included no surgeons, because surgeons routinely recommend and use antimicrobial cleansing products.

The Commissioner recognizes that antimicrobial ingredients are contained in marketed surgical scrubs that are used by surgeons, but does not believe that including surgeons on the Panel would have substantially improved the reliability of the advice rendered. Judgments about the safety and effectiveness of antimicrobials are made on the basis of microbiological, toxicological, epidemiological, and biostatistical data. The Panel members were qualified to judge such data in fact cited scientific literature published by surgeons. In addition, the procedures employed for developing the monograph include opportunities for surgeons to express their views. The Panel itself requested advice from the appropriate committee of the American College of Surgeons, but received no response.

15. Numerous comments referred to the hypothesis that elimination of gram-positive skin bacteria is inevitably followed by shifts in environmental pressures toward gram-negative bacteria. They contended that the concept is not supported by a preponderance of existing evidence, and that, therefore, the danger that might exist from the postulated phenomenon is speculative. Comments cited scientific literature to support the claim that gram-negative bacterial overgrowth after use of an antimicrobial soap is a theoretical expectation not verified by experience. The existence of an unsubstantiated hypothesis provides no scientific or legal justification for banning the normal household use of antimicrobial soap, the comments argued.

The Panel's statements did not imply the inevitability stressed in the comments, but rather were intended to call attention to the published literature indicating such a potential and to encourage studies of the normal flora balance. A few studies completed since the Panel's report have verified that shifts, and more probably, simplifications, of flora do occur.

The Commissioner advises that the nature and quantity of evidence required to support a judgment of safety and effectiveness is determined on the merits of the individual case. The unproven hypothesis that danger may exist in particular circumstances does not, in itself, constitute a sufficient basis for banning the use of a product. The Commissioner is aware of the theory that gram-negative bacteria, which may be undesirable, will replace gram-positive bacteria that are reduced in number or eliminated by use of an antimicrobial soap. The theory is still the subject of experimentation, documentation, and debate. The Commissioner encourages research aimed at testing the validity of the theory with reference to the use of OTC antimicrobial products.

The Panel has served a useful purpose in highlighting the need for research on the microbial ecology of the skin. The Panel was concerned with the need to understand the factors involved in maintaining the balance among species of microorganisms that constitute the normal skin microflora. This balance is more likely to be threatened by overuse of antimicrobials with a limited spectrum than by broad-spectrum antimicrobials, and the imbalance can involve certain gram-positive bacteria and fungi as well as gram-negative bacteria.

The Panel was particularly concerned about the effect of overuse of antimicrobial products in closed populations, such as hospitals or nursing homes, where a variety of ecological pressures combine to favor the growth of gram-negative organisms. In such health care facilities, gram-positive organisms are often drastically reduced by the use of disinfectants, antibiotics, and other antimicrobial products with limited spectra that are effective against gram-positive organims, but not against gram-negative organisms, such as *Pseudomonas*. Serious effects can be expected in severely debilitated patients or in patients at high risk, such as burn victims, the elderly, and newborns, if gram-negative organisms are encouraged to multiply unchecked by the selective eradication

of gram-positive organisms. The results can be devastating.

The Commissioner concludes that professional labeling (labeling for health professionals but not for the general public) for certain antimicrobial ingredients approved for OTC drug use, but primarily used in health-care facilities, should therefore state: *"Caution*: Overuse of this and other antimicrobial products may result in an overgrowth of gram-negative organisms, particularly *Pseudomonas*. These effects could be serious in severely debilitated patients or patients at high risk, such as burn victims, the elderly or newborns."

However, it is the conclusion of the Commissioner that the limited consumer use of antimicrobial-containing products under normal conditions in the population at large does not constitute a risk that would warrant the above label warning or removal of such products from the OTC marketplace.

16. A comment referred to evidence that the gram-positive bacterial flora of skin cannot be considered entirely nonpathogenic. The comment asked for modification of the Panel's statement in the report that gram-positive staphylococci on the skin that are coagulase negative are regarded as harmless.

The Commissioner agrees that the gram-positive flora of the skin cannot be considered totally benign. Scientific literature recognizes a correlation between the ability of staphylococci to cause disease and their ability to produce the enzyme coagulase. However, some staphylococci that are unable to synthesize coagulase are pathogenic and have been implicated in a number of disease conditions, including bacterial endocarditis and soft tissue infections.

17. Several comments discussed the relationship of the type of microbial flora to production of body odor. The comments asked that a quantitative standard for reduction of the total count of microbes as an index of deodorancy not be fixed. The comments based their criticism on the absence of a known exact correlation between a decrease in total microbial count and odor reduction.

The Commissioner recognizes that reduction in total microbial count is not necessarily correlated with deodorancy. Yet the use of an antimicrobial in a deodorant soap is based on knowledge that microbial metabolism is responsible for production of offensive body odor. It is also true that the specific contributions of particular species of microorganisms to odor production vary and that the predominant species of organism contributing to a total count of organisms in a laboratory procedure may not be the primary agents involved in odor production. On the other hand, antimicrobials employed in soap are not so specific in their activity as to inhibit or kill only those organisms responsible for odor production. Consequently, while a perfect correlation between reduction of the number of microbes and decrease in body odor does not exist, it is reasonable to use a general decrease of antimicrobial activity to establish the deodorancy effectiveness of an antimicrobial soap.

The Commissioner concludes that claims of effectiveness of antimicrobials as deodorants will be accepted if they are based on a direct demonstration of odor reduction correlated with either a reduction in total microbial count of one log ($\log_{10}$) or a significant inhibition of microbial species shown to be responsible for odor production. The Commissioner intends that the testing guidelines include these testing procedures.

18. A number of comments objected to the restriction on the use of antimicrobial soaps in the first 6 months of neonatal life as being arbitrary. The comments stated that skin and other infections in infants require that antimicrobial soaps be used in the nursery.

If an antimicrobial is safe because it is not absorbed from the skin, or because the amount absorbed is nontoxic or is capable of being excreted by normal mechanisms, then there would be no reason to ban the use on neonates of a soap containing an antimicrobial. If, however, the safety of an antimicrobial depends for its detoxification and excretion on an enzymatic action or other mechanism that is not fully operative in the newborn, then an antimicrobial should not be used until the infant has matured. It is also proper, given reasonably expected deviations from the average for all infants, to caution against the use of an antimicrobial until a "safety factor of time" has elapsed after the point at which the typical infant's detoxification and excretory mechanisms have become fully effective. The magnitude of the appropriate safety factor is a matter of informed judgment rather than established scientific fact, and a decision about its length should err on the side of caution. The Commissioner therefore accepts the Panel's recommendation that antimicrobial soaps not be used in the first 6 months of neonatal life, subject to evidence from studies suggested in the testing guidelines that show that the 6-month restriction is not required to fully protect these infants. In addition, the Commissioner sees little or no need to use antimicrobial soaps on infants. Also, though he is aware that recent studies on triclosan in rhesus monkey neonates indicate an alternate metabolic pathway, he cannot be completely assured that, when the major metabolic pathway (the glucuronide pathway) is unavailable or saturated, the metabolic system can adapt to excrete active ingredients contained in antimicrobial soaps by either sulfonation or some other metabolic route. Accordingly, labeling for antimicrobial bar soaps will be modified to reflect this condition of use by including the warning, "Do not use this product on infants under 6 months of age".

The Commissioner also wishes to note that he has received a petition to delete the general labeling requirement in § 330.1(g) (21 CFR 330.1(g)) for antimicrobial bar soaps. This section states:

Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a Poison Control Center immediately.

The Commissioner has carefully reviewed the safety considerations relating to any possible way that young children could ingest a sufficient quantity of such soaps to result in toxic or life-threatening reactions. He concludes that it is virtually impossible for a child to ingest a sufficient quantity of any antimicrobial soap to result in toxic symptoms without first inducing emesis. Accordingly, the Commissioner will grant this petition and amend the tentative final monograph to exclude the labeling requirement of § 330.1(g) for antimicrobial bar soaps.

19. A comment expressed concern that the recommendation of the Panel of a 100-fold safety factor as guidance in evaluating antimicrobials would be made a rigid requirement.

The Panel statement does provide for flexibility. The Panel took into account common practice in the field of toxicology, which has been to use a 100-fold safety factor. The Panel recognized that such a limit was a matter of both of knowledge and of judgment, and in considering this particular safety factor for antimicrobials, it drew upon experience and custom. The Panel also recognized that the safety factor used in a given case should reflect the gravity of the adverse effects anticipated and the amount of data available from human studies. The Commissioner will retain a minimum of a 100-fold safety factor applied to the exposure dose for ingredients in products labeled for repeated daily use, i.e., antimicrobial soaps, health-care personnel handwashes, and surgical hand scrubs. Modifications of the safety factor will be allowed for specific ingredients where justified by risk-benefit considerations and where requests are based on submitted data.

20. A comment objected to the Panel's calculation of safety factors for human dosage levels based upon extrapolation of surface area calculations in animals.

The Panel was aware of the limitations of extrapolation from oral doses per kg weight to surface areas for comparing toxic effects among different animal species, but surface area is commonly used in the scientific community to estimate and compare toxic effects of compounds in different mammalian species. Indeed, surface area is a particularly appropriate factor for comparing the toxic effects of substances for topical application.

Because the Panel's method of extrapolation is scientifically reasonable and because no better method of extrapolation is proposed by the comment, the Commissioner concludes that the Panel's recommendation should be retained.

B. COMMENTS ON DEFINITIONS

21. A comment discussed the Panel's definition of active "antimicrobial ingredient": "An agent which kills or inhibits the growth and reproduction of microorganisms" (39 FR 33107). The comment stated that the Panel discussion is not clear and leads to illogical and bizarre results. The comment suggests

the following definitions for an active antimicrobial ingredient: "The active ingredients of an antimicrobial product are those ingredients which contribute functionally to the uses of that product claimed in its label. An active antimicrobial ingredient is an agent which, when appropriately formulated and used, kills or inhibits the growth and reproduction of micro-organisms."

The comment poses two basic problems: First, the need for a clear definition of active versus inactive ingredients; second, some clarity in the basic definition of "antimicrobial."

As to the first point, the Commissioner agrees with the comment that for regulatory purposes, the dividing line between an active antimicrobial ingredient considered as a preservative is dependent upon the relationship of the ingredient to the claim(s) that appear in the labeling of the product. The Commissioner, therefore, defines an "active" antimicrobial ingredient as a compound or substance that contributes to the claimed effect of the product. An "inactive" antimicrobial ingredient is defined as an antimicrobial agent that is included in a product strictly as a preservative for the product itself (at concentrations below those set forth in this document) and that does not contribute to the claimed effect(s) of the product.

As to the second point, the Commissioner believes that by highlighting the difference between active and inactive antimicrobial ingredients, he has clarified the definition of "antimicrobial" and that the definition of an active (antimicrobial) agent proffered in the comment is somewhat ambiguous due to inclusion of the phrase "contributes functionally."

Accordingly, the Commissioner is adopting the following definitions in § 333.3 of the tentative final monograph:

§ 333.3 *Definitions.*

* * * * *

(a) *Antimicrobial (active) ingredient.* A compound or substance that kills microorganisms or prevents or inhibits their growth and reproduction and contributes to the claimed effects of the product in which it is included.

(b) *Antimicrobial preservative (inactive) ingredient.* A compound or substance that kills microorganisms or prevents or inhibits their growth and reproduction and is included in a product formulation only at a concentration sufficient to prevent spoilage or prevent growth of inadvertently added microorganisms, but does not contribute to the claimed effects of the product to which it is added.

* * * * *

22. Two comments stated that the definition of "soap" is "metallic salts of organic fatty acids," a definition which has also been used by FDA, and claimed that the Panel's definition of "antimicrobial soap" could exclude antimicrobial bars containing synthetic detergents. The comments expressed the hope that "there is no intention to exclude" such soap preparations.

The word "soap" has a strict chemical definition, and is also perceived by consumers as any cleanser or product that includes soap (according to the chemical definition) as an essential part of the formulation. The definition of "antimicrobial soap" for purposes of the monograph relates only to the presence or absence of an antimicrobial ingredient, not to the manner in which "soap" generally is formulated.

The Commissioner concludes that soap formulations containing synthetic detergents are within the scope of the term "antimicrobial soap" if they also contain an antimicrobial ingredient.

23. A comment suggested that antimicrobials not intended for repeated daily use, and that skin antiseptics, for example, should have a label statement limiting the number of days during which the product should be used without visible improvement in the user's condition, and emphasizing the need to consult a physician after that time.

Although the Commissioner believes that OTC products should be available for symptomatic relief of normally self-limiting conditions that can be diagnosed by a lay person, he agrees that labeling should warn that, if complications arise or if the diagnosis appears to have been incorrect because the condition fails to improve, the lay person should seek appropriate professional treatment.

Accordingly, the Commissioner concludes that the following warning will be required on labeling of skin antiseptics, skin wound cleansers, and skin wound protectants: "Do not use this product for more than 10 days. If the infection worsens or persists, see your physician." The time limit was chosen on the basis of the average length of time for the completion of the normal healing process for a minor wound, which has been reported by Anderson to be 7 to 10 days (Anderson V., "Over-the-Counter Topical Antibiotic Products: Data on Safety and Efficacy," supplement to *International Journal of Dermatology*, 15:1–118, 1976). In addition, the Commissioner concludes that all product categories (other than antimicrobial bar soaps) should contain the warning, "For external use only."

24. A comment suggested that the definition of antimicrobial soap in § 333.3 (a) of the proposed monograph (§ 333.3 (c) in the tentative final monograph) be changed by deleting "in vitro."

The Commissioner agrees with the Panel that there is a need to include results of in vitro testing to delineate or characterize activity of an ingredient as an antimicrobial. Results of in vitro testing will then give some guidance by which safety and effectiveness tests can be confirmed in later in vivo testing. The Panel's definition will therefore be retained because it is more inclusive than the one suggested in the comment.

However, the comment has also raised a problem with regard to inclusion of definitions in labeling. The Panel recommended that any phrase(s) used in definitions of the various product classes be permitted in labeling. Although some of the phrases in the definitions would add clarity to the claims for these product classes, the inclusion of phrases such as "in vitro" or "in vivo" in antimicrobial soaps would not be informative and would likely be misleading. Accordingly, the Commissioner will modify the Panel's recommendation in the monograph to include only selected phrases from the product class definitions. The monograph will provide for specific labeling indications and other allowable statements.

25. A comment asked that additional terms be allowed for labeling of the product category "antimicrobial soap." The additional terms requested are those presently suggested by the Panel for the category "health-care personnel handwash": "decreases bacteria on the skin, reduces risk and/or chance of cross-infection, recommended for repeated use."

The Commissioner notes that products in the category of "health-care personnel handwashes" are intended to serve a different purpose than products in the category "antimicrobial soaps." "Health-care personnel handwashes" are intended to be used as often as 50 to 100 times daily by a single user. They are also intended for use in a hospital setting by health-care personnel who understand the need for almost constant removal of transient flora to prevent cross-infection between patients. Labeling for this product category has been designed to have maximum meaning for these individuals.

By contrast, antimicrobial soaps are intended to be used by the general public only in nonhospital settings. In fact, antimicrobial bar soaps are frequently banned in many hospitals because they may promote cross-contamination. The different circumstances of use require different labeling for these two types of products.

Moreover, use of terms permissible for health-care personnel handwash products could be confusing or misleading to the average member of the lay public. The statement "recommended for repeated use" would mean little to the average consumer, though it has specific meaning for health-care personnel who may wash 50 to 100 times a day and who thus require a product that will not be irritating. The statement would be inappropriate for an antimicrobial soap; safe antimicrobial ingredient levels in antimicrobial soaps are established by reference to use a few times daily, not 100 times daily.

"Reduces risk and/or chance of cross-infection" does not relate to the circumstances of use by the average consumer and would instill in him a false expectation of greater health benefits. Health-care personnel ascribe much more specific meaning to this claim.

"Decreases bacteria on skin" applies literally to both an antimicrobial soap and a health-care personnel handwash (provided it contains an antimicrobial). However, this type of claim could be misleading to the lay person unless accompanied by clarifying language, such as "decreases bacteria on the skin which cause odor." Absent such a qualification, the Commissioner believes, the average consumer could mistakenly conclude

that a decrease in bacteria necessarily signifies a decreased likelihood of infection. This could lead an individual who develops a minor infection in a skin wound to use an antimicrobial soap instead of a skin antiseptic. Accordingly, the Commissioner concludes that the additional terms should not be included in labeling for antimicrobial soaps.

26. There was comment that extensive trials conducted with antimicrobial soaps (some containing tribromsalan as an ingredient) to show usefulness in the prophylaxis of minor skin infections support the effectiveness of these products, as do testimonials from recognized experts.

The Panel analyzed the clinical trials that were submitted and published in the scientific literature. The Commissioner concurs with the Panel's conclusion that clinical effectiveness has not been shown unequivocally. Under the requirements of the OTC drug review regulations (21 CFR 330.10(a)(4)(ii)) and section 201(p) of the act (21 U.S.C. 321(p)), opinions of experts, unsupported by adequate and well-controlled clinical investigations substantiating effectiveness, are not evidence of general recognition of effectiveness. It remains to conduct adequate, well-controlled trials to demonstrate clinical effectiveness of these products, as set forth in the testing guidelines.

27. A comment suggested that the definition of health-care personnel handwash in proposed § 333.3(b) be revised to delete the requirements that the products be "nonirritating" and, "if possible, persistent."

The Panel was concerned with the need for frequent, repeated use of these products according to an established regimen intended to reduce the risk of cross-infection in health care facilities. To assure proper use, the products, which may be used as often as 100 times daily, must be nonirritating. Persistence, defined as prolonged activity, is a valuable attribute that assures antimicrobial activity during the interval between washings. The Commissioner agrees with the Panel that these two attributes are important to a safe and effective health-care personnel handwash, and is, therefore, retaining the Panel's definition in § 333.3(d) of the tentative final monograph. In addition, the Commissioner has provided directions for use as follows: "Wet skin and spread a small amount on hands and forearms. Scrub well and rinse thoroughly after washing".

28. A comment objected to permitting a patient preoperative skin preparation to be an OTC product, especially since it is primarily used in hospitals. The reason given was that the surgeon usually "prescribes" for his patient the types of antimicrobial to be employed in preparing the site of incision. It was also suggested that surgical hand scrubs be limited to prescription use because their use is directed or supervised by the practicing surgeon.

"Prescribe" can mean to specify use of a drug legally restricted to dispensation, or simply to specify with authority. It is common for physicians, on the basis of their professional knowledge, to direct the use of various products, such as OTC drugs and certain foods, that are not limited to prescription sale. The OTC or prescription status of patient preoperative skin preparations or surgical hand scrubs, therefore, does not affect the surgeon's ability to control what product will be used to prepare his patient for surgery or by those participating in the procedure. Nor does it relate to the effectiveness of the products. The difference between an OTC or prescription product does not lie in effectiveness, but in whether it can be labeled for safe and effective use by the lay person. Since patient preoperative skin preparations and surgical hand scrubs can be so labeled for use by health care personnel, there is no reason to reclassify them as prescription drugs.

29. A comment suggested that the proposed monograph definitions of skin antiseptic in § 333.3(d), skin wound cleanser in § 333.3(e), and skin wound protectant in § 333.3(f) be changed to delete the requirement that the product classes be nonirritating and that the definitions of skin wound cleanser in § 333.3(e) and skin wound protectant in § 333.3(f) be further revised to delete the requirement that such products do not delay wound healing.

The Panel considered those factors that would assure safety and effectiveness of these products. One of the factors considered was the relationship of irritation to delay in wound healing. The Panel believed, and the Commissioner agrees, that such products should not be irritating because irritation may delay wound healing. Therefore, the term "nonirritating" is retained in the cited definitions, as is the requirement that skin wound cleansers and skin wound protectants not delay wound healing.

The Commissioner has further reviewed the proposed warnings for skin wound protectants and skin wound cleansers. Based upon a review of all the data available, he concludes that the labeling should be revised to the statements proposed in the tentative final monograph below.

30. A comment asked for a judicious rather than an absolute interpretation of the requirement that a skin wound cleanser and a skin wound protectant not delay wound healing. It emphasized that a product may compensate for delay in healing with other benefits, such as pain relief. Similar comments were received regarding the nonirritation requirement for a skin wound cleanser, skin wound protectant, skin antiseptic, surgical hand scrub, and health-care personnel handwash.

The Commissioner recognizes, as did the Panel, that in a definition goals must be stated, and that in arriving at goals, as long as the public health is fully protected, there may have to be compromises because the state of the art does not permit an ideal solution. The Commissioner believes that the comment has merit. In interpreting the Panel's definitions of antimicrobials, the agency will examine the totality of benefits and risks of a specific product and arrive at a decision for categorizing it on the basis of its overall value. Thus, a particular product that causes slight irritation or delays wound healing for a relatively short period can be generally recognized as safe and effective if those side effects are offset by a compensating benefit.

31. A comment stated that the requirement that a skin wound cleanser not delay wound healing is meaningless unless it is compared to something. Since no standard is specified by the Panel, the requirement cannot be met.

The comment is incorrect. The Panel asks for controlled observations or experiments in which the product would necessarily be compared to an objective method. For example, a test might include a comparison of wounds on the same subject: one wound treated with the product minus the antimicrobial ingredient, another wound treated with the product itself. Under the Panel's definition, the test must show that the product is not formulated in such a way as to prolong healing, or it must show that healing delay is minimal and is offset by a compensating benefit.

32. A comment suggested that the proposed monograph definition of skin antiseptic in § 333.3(d) be modified to delete the requirement that claims for activity against specific microorganisms be supported by controlled human studies demonstrating prevention of infection.

The Commissioner agrees. The Panel was aware that there is testimonial evidence for prevention of overt skin infection by skin antiseptics, but that there is an absence of controlled studies to validate this hypothesis. The Panel's intent was to emphasize the importance of proving effectiveness and to eliminate confusion in the use of that term. The Commissioner recognizes and agrees with the Panel's concern for adequate testing; but, in the interest of consistency with the other product category definitions, which do not include the details of testing requirements, the Commissioner is modifying the definition of skin antiseptic to delete the reference to this testing requirement. Controlled human studies to prove effectiveness of skin antiseptics will, however, be required and will be included in the testing guidelines discussed in this document.

33. A number of comments objected to the Panel's definition of skin antiseptic as inconsistent with section 201(o) of the act, which states:

> The representation of a drug, in its labeling, as an antiseptic shall be considered to be a representation that it is a germicide, except in the case of a drug purporting to be, or represented as, an antiseptic for inhibitory use as a wet dressing, ointment, dusting powder, or such other use as involves prolonged contact with the body.

The comments contended that, under this provision, a skin antiseptic need only have germicidal properties and need not demonstrate clinical effectiveness.

The comments erroneously equate the minimum standard of performance established by Congress for products

labeled as antiseptics with the appropriate definition of effectiveness for such products in relation to the standards for determining when drugs are generally recognized as safe and effective. Section 201(o) establishes that, at a minimum, a drug claiming to be an antiseptic must be germicidal rather than merely germistatic or bacteriostatic. That is, it must actually kill the organisms, not merely inhibit their growth and/or reproduction. An exception was made for certain types of drugs, such as wet dressings, where inhibition alone might be sufficient due to prolonged contact with the body. That a product has germicidal properties, i.e., the minimum pharmacologic effect required by section 201(o) of the act, however, does not mean that it is "effective" under section 201(p) of the act. Effectiveness refers to the ability of a drug to achieve its intended purpose. Drugs are generally not considered effective simply because they demonstrate pharmacologic activity; a pharmacologic effect without a corresponding therapeutic benefit is of no use to the patient. Specifically, it is not established that a patient will benefit solely from germicidal action of skin antiseptics, which, therefore, cannot be considered effective within the meaning of the act unless they can be shown to accomplish a useful therapeutic purpose, i.e., prevent skin infection. Accordingly, skin antiseptics must prove effectiveness by means of controlled human studies using the testing guidelines discussed elsewhere in this document.

34. A comment pointed out that "controls infection" is a permissible label term for skin antiseptic, and yet is prohibited in another section of the Panel's report, under "Labeling" (39 FR 33123).

The Commissioner agrees that the inconsistency pointed out in the comment should be corrected. In the Category II discussion below the Commissioner will delete references that this claim is misleading.

35. A comment asked that the phrase "contains antimicrobial ingredient(s)" be permitted in labels for skin antiseptics.

The Commissioner agrees and will permit this term to be used in labeling for skin antiseptics.

36. A comment contended that "evaluations must be restricted to judgment based on the literature and long market experience in the case of skin antiseptics."

The Commissioner concludes that the Panel has acted reasonably and in full accord with the regulations governing this review identified in § 330.10 in requiring that claims be supported by controlled human studies. Specifically, § 330.10(a)(4)(ii) states:

> * * * Proof of effectiveness shall consist of controlled clinical investigations as defined in § 314.111(a)(5)(ii) * * *, unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the drug or essential to the validity of the investigation and that an alternative method of investigation is adequate to substantiate effectiveness. * * *

The comment is in error in stating that "evaluations must be restricted to judgment based on the literature and long market experience in the case of skin antiseptics." The regulation specifically states that "Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered" (21 CFR 330.10(a)(4)(ii)). The relationship of marketing history to effectiveness was discussed in paragraphs 55 through 59 of the preamble to the final OTC drug regulations published in the FEDERAL REGISTER of May 11, 1972 (37 FR 9469), which noted that marketing experience could only be considered to corroborate adequate scientific evidence.

37. A comment objected to defining a skin wound cleanser without a requirement for the presence of an antimicrobial agent. The comment noted that the word "antimicrobial" does not occur in the definition of skin wound cleanser.

The Panel stated that the primary purpose of a skin wound cleanser is to remove foreign material, dirt, and debris (39 FR 33112, paragraph 7). The Commissioner concludes that the Panel's definition, which reflects that purpose, is reasonable. The definition does not preclude incorporating an effective antimicrobial in such products. Moreover, it preserves freedom of choice to the consumer as to whether treatment of a wound will be a two-step treatment (cleansing a wound of debris and foreign matter and subsequently applying an antimicrobial), or a single-step treatment (applying a cleanser combined with an antimicrobial).

The Panel, it should be noted, did not believe that antimicrobials available for addition to a cleanser are effective in the prevention of wound infections. Therefore, to make proof of prevention of infection mandatory in the definition of a skin wound cleanser, as would be necessary if the definition required the presence of an antimicrobial agent, would preclude placing any skin wound cleanser in Category I at this time because the kind of evidence needed for this classification was not available to the Panel.

38. Comments asked for a subcategory of skin wound cleanser that would specifically recognize products containing an antimicrobial.

The Commissioner agrees that the public should be fully informed of the contents of the products it uses. In the case of skin wound cleansers, it is important that the consumer know that an antimicrobial ingredient has been included in such a product. So long as the labeling claims remain unchanged, the Commissioner does not believe that the consumer will be misled by identifying the presence of such an ingredient in the active ingredient section of the label. Accordingly, though the Commissioner will permit the label to state that the product contains an antimicrobial by listing it as an active ingredient subject to the labeling limitations for skin wound cleansers, no subcategory with additional labeling will be permitted.

If a manufacturer wishes to make a broader range of claims for the antimicrobial ingredient in his product, there is nothing that prohibits a product from meeting the requirements applicable to skin antiseptics identified below in § 333.3(f) of the tentative final monograph.

39. A comment objected to the phrase "nor favors the growth of microorganisms" in the definition of skin wound protectant in § 333.3(f) of the September 1974 proposed as superfluous.

The Panel recognized that a skin wound protectant as a physical barrier can exclude contamination, but also that it might itself be capable of being colonized by microorganisms already present in the wound. Thus, there is justification for requiring that the protectant both prevent admission to a wound of microorganisms from the environment and not provide environmental conditions within the wound that encourage growth of microorganisms by alteration of the wound environment itself. The requirement that the protectant not favor the growth of microorganisms is important, given the ability of anaerobic bacteria to establish themselves in a wound. The Commissioner therefore concludes that, except for the changes set forth in paragraph 40 below, the definition of skin wound protectant in § 333.3(h) of the tentative final monograph should remain as recommended by the Panel.

40. A comment pointed out that part of the definition in the Panel's report that a skin wound protectant must act as a physical barrier is not consistent with the monograph's definition referring to either physical or chemical barriers to infection.

The Commissioner believes that the comment has misinterpreted the requirements of a skin wound protectant. Such products were intended to serve as a barrier against contamination of a cleansed wound. The Panel through its definition of skin wound protectant and its discussion of skin wound protectants in the testing guidelines of their report (39 FR 33140) attempted to make clear its view that this class of products must in all cases provide a physical barrier for minor wounds and might also contain an antimicrobial ingredient, a "chemical barrier," to inhibit growth of microorganisms that might remain after a wound is cleansed. These products might include the antimicrobial ingredients reviewed by this Panel, or topical antibiotic ingredients now being reviewed by the OTC Antimicrobial II Panel, or ingredients now being reviewed by the OTC Miscellaneous External Drug Products Review Panel. It is even possible that the latter Panel might suggest nonchemical ingredients to be used solely as physical barriers. However, the Panel made no recommendations on skin wound protectants with only physical barriers. Unless and until such recommendations come to the Commissioner's attention, skin wound protectants must

be viewed as products that provide both a physical and a chemical (antimicrobial) barrier to cleansed small wounds. Accordingly, for purposes of this tentative final monograph, the word "and" is substituted for the words "and/or" in the definition of skin wound protectant identified in § 333.3(h); the paragraph thus refers to "a protective physical barrier and a chemical (antimicrobial) barrier."

41. A comment suggested modifying the directions for use of skin wound protectants to delete the statement "cleanse wound thoroughly before applying."

The Panel's discussion made it clear why it is necessary to cleanse wounds of debris and extraneous foreign matter before application of a skin wound protectant. The Commissioner believes that the consumer should be informed of the requirements for self-care of wounds. Accordingly, the Commissioner is retaining the Panel's suggested language, with slight modifications for clarity.

42. A comment suggested that the definition of surgical hand scrub be revised to delete the requirement that the product be nonirritating.

As noted in the response to comments in paragraphs 29 through 31 above, irritation may have an adverse effect on wound healing. Although surgical hand scrubs are not intended for treatment of wounds, the surgeon or other healthcare personnel often wash frequently with such a product. If the product has the property of causing irritation it would be unsuited for use as a surgical hand scrub. Consequently, the Commissioner is retaining in the tentative order the Panel's requirement that the product be nonirritating. He is also providing labeling indications and directions for their use in the tentative final monograph.

C. COMMENTS ON COMBINATIONS

43. Several comments, citing the OTC drug combination policy set forth in § 330.10(a)(4)(iv) (21 CFR 330.10(a)(4)(iv)), objected to what was perceived as a requirement in the Panel report that combinations of antimicrobials be synergistic in their activity.

The Commissioner advises that the Panel recognized synergism as one justification for combining antimicrobials, but not the only one. Section 330.1(a)(4)(iv) requires that a combination of active ingredients be at least as active as each single ingredient would be separately and that each ingredient make a contribution to the claimed effect(s). A combination of antimicrobials will be recognized as safe and effective when the combination does not decrease the safety and effectiveness of the individual active ingredients. The contribution of an ingredient to the effectiveness of a combination must be measurable in some manner. The Commissioner reiterates current FDA policy that a combination product must be as safe as its constituent ingredients alone.

44. Several comments stated that the criteria in the Panel's report (39 FR 33106) for antimicrobial ingredients combined with nonantimicrobial ingredients are unclear. The comment requested that, since the monograph does not "provide for the combination of antimicrobial ingredients with active nonantimicrobial ingredients," a new subsection be added to the monograph stating that "an antimicrobial may be combined with any generally recognized as safe and effective nonantimicrobial ingredient(s) if it is indicated for use safely for the condition indicated for the ingredients," and that the requirements of the Panel's five criteria be clarified.

The Commissioner agrees that the five criteria established by the Panel for combinations of antimicrobial and nonantimicrobial active ingredients are lacking in detail. However, the criteria must be somewhat general and theoretical because, at present, no such combinations are known to exist. The Commissioner, at this time, therefore rejects the suggestion of adding an additional subsection to the monograph. Petitions to amend the monograph that deal with specific combination products would, of course, be considered. The Commissioner concludes that it is not feasible or necessary to clarify the Panel's criteria until such combinations are submitted to the agency in the form of petitions to amend the OTC topical antimicrobial monograph.

D. COMMENTS ON PRESERVATIVES

45. Many comments expressed concern that preservatives limited to the minimum inhibitory concentration as determined in accordance with the *United States Pharmacopeia* (USP) XVIII (p. 845, "Antimicrobial Agents—Effectiveness Test") would not be effective in practice. They argued that the USP procedure is inadequate for the following reasons:

The test was designed for ophthalmics and parenterals and is not suitable for topical preparations intended for repeated use. Repeated use means repeated entry into the container with accompanying opportunity for contamination by a great variety of microorganisms.

No single test for assessing a preservative is adequate because of the great differences in formulation of OTC topicals and the variety of uses of OTC topicals.

The test is inadequate for products with a long shelf life.

The same comments suggested using either the 1973 Cosmetic Toiletry and Fragrance Association (CTFA) preservative test or the proposed preservative test of Committee E–35 on Pesticides of the American Society for Testing and Materials (ASTM). All the comments sought guidance on which preservative tests are acceptable to the agency for these classes of products.

The Commissioner has carefully reviewed the background of the Panel recommendation and the objections to using the "Antimicrobial Agents—Effectiveness Test" of USP XVIII as the sole standard for judging the minimum inhibitory concentration of preservatives. The Commissioner notes that since the publication of the Panel report, the USP test was modified by the nineteenth revision of the USP (USP XIX), effective July 1, 1975, and is now referred to as the "Antimicrobial Preservatives—Effectiveness Test." The Commissioner believes there should be flexibility in test requirements for setting the minimum inhibitory concentration of preservatives. The Commissioner therefore concludes that the procedures described in the USP XIX (P. 587, "Antimicrobial Preservatives—Effectiveness Test") or the CTFA preservative tests published in 1970, both with appropriate modifications, may be employed.

Appropriate modifications to the USP XIX test include the addition of a rechallenge procedure, as well as inclusion of the requirement of "organic load." These modifications are intended to test the ability of the preservative to keep the product from spoiling or becoming heavily contaminated with microorganisms under stress conditions. The rechallenge procedure simulates conditions produced by the common multiple-usage container, which involves frequent reentry by the user. The organic load requirement is a test in which a small quantity of horse serum or killed yeast cells simulates actual use conditions involving contamination with dirt or oil from the hand that results from frequent use.

Appropriate modifications to the 1973 CTFA preservative test include addition of specific microorganisms to be used in the test as well as interpretative criteria.

Both modified preservative tests will be placed on file in the office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857. The Commissioner believes that the objections raised in this comment are met by requiring use of the CTFA and USP XIX testing requirements as modified.

The Commissioner notes that a collaborative study of the proposed preservative test of Committee E–35 on Pesticides of the ASTM is underway, but results are not yet available. Furthermore, this test is designed to test chemical ingredients that are proposed for formulation as a preservative and would not be entirely appropriate for preservative systems and/or testing of formulated products. Therefore, the Commissioner believes only the CTFA and USP XIX tests as modified are appropriate.

46. A comment objected to the "establishment of a uniform specific maximum preservative level for all products which completely ignores the factors of use pattern, dosage form, formula, and the particular microbial contaminants encountered in the manufacturing process of raw materials."

The comment misunderstands the intent of the Panel, which stated that "If an antimicrobial ingredient is to be used as a preservative, evidence should be available to demonstrate that the concentration used is the minimum at which it is effective as a preservative" (39 FR 33106). That is, a given ingredient can be used at different concentrations for preservative purposes in different products. What must be available for inspection is evidence that the concentration used in a particular product

is safe and is the minimum effective concentration. This is stated in § 333.65 of the tentative final monograph below, which provides that "All antimicrobial ingredients used singly or as part of a preservative system * * * shall be tested by the manufacturer to establish the minimal effective preservative concentration for every product formulation * * *."

47. A comment objected to the Panel's recommendation to prohibit use, as preservatives, of antimicrobials placed in Category II. It was noted that one such substance, hexachlorophene, is permitted under § 250.250(d) (21 CFR 250.250(d)) as a preservative, because at the preservative dosage level it is not toxic and is very effective. The comment argued that other antimicrobials might also be safe for use as preservatives even though they are not considered safe for use as active ingredients.

The Commissioner appreciates the concern that sufficient ingredients be available for use as preservatives to assure that products are uncontaminated with microorganisms. The comment correctly states the agency's position that even if ingredients are unsafe at active concentrations they may be employed as preservatives if at those concentrations no hazard exists. However, the Commissioner notes that § 250.250 (d) states that hexachlorophene is only permitted to be included as a preservative where other preservatives are not available and when it is part of a preservative system, not by itself.

Accordingly, the Commissioner will accept use of a Category II ingredient as a preservative, but only if the following conditions are met: It is not a carcinogen, a significant contact sensitizer, or a photosensitizer; it acts as a preservative at concentrations below those causing pathology in mammals; and no adequate substitute is available. Such data must be submitted to the agency in the form of a petition to amend the OTC topical antimicrobial monograph to permit use of such ingredients at preservative levels.

48. A comment stated that contrary to the statement of the Panel (39 FR 33106), methylparaben and propylparaben were not listed as active ingredients by the manufacturer who submitted the data referred to in Reference 1 (OTC volume 020054). The comment further contended that these compounds should not be subject to review by the Panel because FDA on September 23, 1974, affirmed their generally recognized as safe (GRAS) status, under the food additive provisions of the Federal Food, Drug, and Cosmetic Act, at a maximum level of 0.1 percent in food. According to the comment, the use of methylparaben and propylparaben at concentrations of 0.18 and 0.02 percent, respectively, in the formulation in question need not be further evaluated because, in topical application, the amounts absorbed would be less than those absorbed orally at the levels FDA has found acceptable for food.

The Commissioner advises that while these compounds were not listed on the manufacturer's label, they were listed in the formula information submitted to the Panel. There was no differentiation between active and inactive ingredients in this formula, and the Panel assumed that the manufacturer had considered them active ingredients. As the comment points out, this was a misunderstanding since both the manufacturer and the Panel considered both these ingredients to have only a preservative function at the concentrations found in the submitted product. In fact, the Panel clearly acknowledged the preservative function of the parabens in the list of antimicrobial preservatives that it suggested by deferred to and reviewed by the OTC Antimicrobial II Panel (39 FR 33106). However, the Commission has determined that review of inactive ingredients, such as preservatives, is not possible within the present framework of the OTC drug review. With its limited resources, the OTC drug review can presently evaluate only active ingredients, i.e., ingredients for which therapeutic claims are made. Consequently, though the Commissioner appreciates the suggestion of the OTC Antimicrobial I Panel that preservatives be reviewed, he advises that currently it is not possible to do so.

Further, the comment is incorrect that affirmation of a substance as GRAS for food use resolves all safety questions about its drug use. For example, although the parabeans are not sensitizing when ingested with food, they may sensitize skin when applied topically. Because of these safety considerations, the parabens may be reviewed by appropriate OTC advisory review panels.

49. A comment stated that it was not clear from the original charge that this Panel would review preservatives, or that the same safety and labeling standards would be applied to preservatives as to active antimicrobial levels of ingredients, and requested that oxyquinoline sulfate be submitted to the OTC Antimicrobial II Panel for review, with opportunity to present data to that Panel.

The Panel recognized that the issue of preservatives is difficult. The question, however, was not one of effectiveness and labeling so much as one of determining the dividing line between active ingredients and preservatives.

Although the Panel report states (39 FR 33106) that oxyquinoline sulfate and the question of preservatives in antimicrobials should be deferred to the OTC Antimicrobial II Panel for review, the Commissioner, as noted in paragraph 48 above, has determined that a review of inactive ingredients, such as preservatives, is not possible within the present framework of the OTC drug review.

E. COMMENTS ON QUATERNARY AMMONIUM COMPOUNDS

50. Numerous comments objected, and cited exceptions, to two of the Panel's generalizations about quaternary ammonium compounds: that the quaternary ammonium compounds are inactive against gram-negative bacteria, and that modifications of a quaternary ammonium compound molecule lead to predictable antimicrobial and toxicity changes.

Concerning statements about the general characteristics of quaternary ammonium compounds, the language of the Panel was reasonable. The Commissioner agrees, however, that the language in the discussion of Category III ingredients relating to the quaternary ammonium compounds should be modified to make it clear that the characteristics of newly synthesized quaternary ammonium compounds should be modified to make it clear that the characteristics of newly synthesized quaternary ammonium compounds are not always accurately predictable and that gram-negative bacteria may not always be resistant to the quaternary ammonium compounds.

51. A comment objected to Panel statements that outbreaks of gram-negative bacterial infections, as well as other kinds of infection, have been reported as the result of contamination of solutions of quaternary ammonium compounds in laboratory and hospital environments. The comment said that such examples of pathology could just as easily be attributed to misuse, improper storage, or contamination of the quaternary ammonium compound solution with neutralizing chemicals.

The comment correctly notes that outbreaks of infections have been reported as part of the clinical experience associated with these antimicrobials. It appears that practices in the health-care facility environments where quaternary ammonium compounds are commonly used often fall short of the minimum necessary to prevent outbreaks of infection. It should be noted that the Panel was obliged to recognize that though the quaternary ammonium compounds have useful properties, such as nonirritancy, these benefits are often offset by poor sanitary practices or by lack of knowledge about the limitations of these ingredients. For example, though discussed in the September 1974 preamble to the proposal (39 FR 33131), it is not generally known that some quaternary ammonium compounds are inactive in hard water, and some are rendered ineffective in the presence of acidic solutions commonly found in laboratory and hospital environments. The Panel also noted that cationic "quats" are also inactivated by anionic compounds, soaps, Tween 80, and sodium lauryl sulfate as well as by certain metallic ions. Advocacy of use of quaternary ammonium compounds should properly recognize these limitations through adequate label warnings. With some slight modification of language in the Category III discussion below, the Commissioner accepts the Panel discussion as a judicious warning against uncritical use of the quaternary ammonium compounds.

In addition, the tentative final monograph requires that labeling of concentrated products containing quaternary ammonium compounds include the following warning: "Dilute with distilled water before use because acidic or hard water may render the product inactive".

Also, for products distributed only to professionals the Commissioner is including in § 333.99 of the tentative final monograph the warnings: *"Caution:* Overuse of this and other antimicrobial products may result in an overgrowth of gram-negative organisms, particularly *Pseudomonas*. These effects could be serious in severely debilitated patients or patients at high risk such as burn victims, the elderly or newborns" and "this product is rendered inactive by hard water, acidic water, anionic compounds, soaps, Tween 80, and sodium lauryl sulfate".

52. A comment stated that there is ambiguity in " calculating the use concentration for quaternary ammonium compounds as skin wound cleansers in aerosol form," as suggested in the Panel's report. The comment requested that calculation of the use concentration be permitted on a weight-in-weight basis. The comment referred to a similar weight-in-weight calculation for hexachlorophene (21 CFR 250.250) as a precedent for using it as a standard method of calculation.

Because quaternary ammonium compounds are usually diluted to a use concentration and because that concentration is calculated on a weight-in-weight basis, the Panel, in its discussion of these ingredients (39 FR 33116 and 33131), most likely assumed that readers would be familiar with this calculation. In any event, the comment points out an ambiguity in the calculations of the use concentration of the ingredients that requires clarification.

The Commissioner concludes that the weight-in-weight calculation is an acceptable method for specifying the concentration of quaternary ammonium compounds.

However, the Commissioner notes that there is a question about whether the propellant for an aerosol should be considered in the weight-in-weight calculation. The Commissioner concludes that to consider the propellant in this calculation could lead to potential safety problems since, as the propellant evaporates, the concentration of the residual active ingredient increases and could possibly reach high levels. This is particularly a problem for aerosolized quaternary ammonium compounds. Accordingly, propellants may not be considered as part of the weight-in-weight calculation of the concentration of any active ingredient in aerosolized form.

53. One comment noted that the Panel had placed quaternary ammoniun compounds in Category I at a use concentration not greater than 1/750 (39 FR 33116). The comment requested that the Panel's reference to 1/750 in the Category III discussion of quaternary ammonium compounds (39 FR 33132) be considered as not having "substantive significance", and that other use concentrations be permitted in Category III.

The Commissioner does not interpret the Panel's statement as prohibiting concentrations of quaternary ammonium compounds greater than 1/750 if their use is shown to be safe and effective. The Panel statement was merely intended as a guide, with minimum and maximum use levels to be established at such time as sufficient data are generated to place these compounds in Category I. However, when the Commissioner considers data submitted under the testing guidelines for quaternary ammonium compounds, he will require the minimum and maximum concentrations of those compounds to be included in the monograph.

54. A comment cited the existence of newer quaternary ammonium compounds whose antimicrobial activity is not adversely affected in the presence of acidic or hard water. It was asked that the existence of such quaternary ammonium compounds be recognized.

The Commissioner is aware of the existence of quaternary ammonium compounds that can act as antimicrobials in acidic and hard water environments and has acknowledged their existence in the discussion of quaternary ammonium compounds elsewhere in this document. He also recognizes that not all quaternary ammonium compounds are similar in this regard. To alert the consumer to how individual quaternary ammonium compounds behave in different environmental conditions, labeling of these antimicrobials will be required to include the statement of their effectiveness in the presence of acidic or hard water, as set forth in the response in paragraph 51.

55. A comment objected to the statement in the report that quaternary ammonium compounds are inactive against the gram-negative bacteria *Pseudomonas*.

The Commissioner is aware that some quaternary ammonium compounds at very high concentrations can inhibit or kill *Pseudomonas*. The Panel concluded, however, that the concentrations required are so high that they are very irritating and not desirable for use on the skin. But the Panel statement does not preclude the Commissioner from approving any new quaternary ammonium preparation at any concentration that is safe and effective against *Pseudomonas*.

56. A comment pointed out that the quaternary ammonium compounds have been classified as generally recognized as safe and effective for antiseptic use by the OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Treatment and Prevention Panel. Recognition of a new class of antimicrobials, "minor antiseptics," to include these compounds was suggested by the comment.

It is premature to anticipate inconsistency on this question between the two Panels. The OTC Topical Analgesic Panel will most likely direct its review of antimicrobial agents toward the effects of products or infections accompanying burns or sunburns, and will be aware of the OTC Antimicrobial I Panel's findings. The OTC topical analgesic final report will therefore be prepared with this report in view, and any conflicts can be eliminated at that time.

The Commissioner rejects as unnecessarily confusing the suggestion for a category of "minor antiseptics." It would increase the number of categories of antimicrobial products with no compensating gain. Further, defining a new category of antimicrobial products does not reduce the amount of evidence needed to establish safety and effectiveness.

57. A comment suggested that the section of the proposed monograph dealing with labeling for skin wound cleansers containing quaternary ammonium compounds (proposed § 333.90, redesignated § 333.92 below) be revised to read as follows:

§ 333.90 *Skin wound cleanser.*

* * * * *

(b) *Warnings.* The labeling for quaternary ammonuim products marketed as concentrates contains the following warnings:

(i) Caution: May cause eye irritation or damage unless diluted.

(ii) Dilute before each use to avoid spoilage.

(iii) Do not bandage tightly as to exclude air.

The labeling for quaternary ammonium products marketed at use concentration contains the following warnings:

(i) Do not bandage tightly.

The labeling for this product shall contain the recommended dosage for use and the method by which the product shall be used in preventing overt infection due to organisms against which the product is effective.

* * * * *

The Commissioner agrees that the format of this section should be revised, as suggested, to more clearly distinguish between warnings required for products intended as concentrates and products marketed at use concentrations. The Comimssioner further agrees that the Panel's recommended warning against "occlusive dressing" is more comprehensibly phrased in terms of tight bandaging, and is therefore adopting, with slightly modified wording, the suggestion in the comment. The warning "Do not use solution with occlusive dressing" may be substituted, however, in labeling of products intended for distribution to health care professionals.

The Commissioner does not agree that the directions-for-use requirement recommended by the Panel is improved by the change suggested in the comment. The tentative final monograph requires that labeling contain the statement "Apply to affected area" and a statement of the recommended dosage for use and method by which the product shall be used to cleanse a small wound without further damage to the injured area. The Commissioner concludes that directions for use that conform to these requirements will be more instructive to the user than directions for use that meet the more general requirements suggested in the comment.

58. A comment contended that a particular mixture of three benzalkonium halide compounds with varying chain lengths meets the definition and requirements of a surgical hand scrub, and that as a result the Panel condemnation of all quaternary compounds as not having broad spectrum antimicrobial activity is not accurate. The comment further pointed out that the combination

differs significantly from the characteristics of the quaternary ammonium compounds that formed the basis for the Panel's generalization, i.e., benzalkonium chloride, benzelthonium chloride, and methylbenzethonium chloride.

The benzelkonium halide compounds in the product referred to in the comment are similar to benzalkonium chloride, which was reviewed by the Panel. None of the compounds was submitted to or reviewed by the Panel. The data in the comment were fragmentary and based on tests designed for disinfectant sanitizers subject to the Environmental Protection Agency's regulations for disinfectants. The Commissioner is not aware that the compounds have been subjected to the testing required to establish general recognition of safety and effectiveness for topical antimicrobial products, which is set forth in the testing guidelines below.

In addition, the data submitted in the comment do not establish a significant difference in safety or effectiveness from the quaternary compounds reviewed by the Panel. For example, the effectiveness data do not establish any difference in spectrum from the quaternaries discussed in the Panel's report.

For the above reasons, no modification of the Panel's statements relating to the limitations on quaternary ammonium compounds is required. The three ingredients discussed in the comment are placed in Category III. They will have to be tested separately and as a combination under the testing guidelines to fully determine general recognition of safety and effectiveness for OTC antimicrobial use.

F. COMMENTS ON CLOFLUCARBANS

59. A comment stated that the further rat-feeding studies requested by the Panel are unnecessary for cloflucarban because data on file in the OTC submissions, and in a submission to the master file record, contain adequate data on toxicity. The comment claimed that although the Panel stated that inadequate data were presented, and referred to testicular effects of cloflucarban on male rats, the data were preliminary and not confirmed by the additional data later reported to the agency. The comment went on to note that the Panel was "incorrect in stating that changes (testicular) occurred in the Cox rat at 1,000 mg/kg since such a dose was not used."

The Commissioner has reviewed the data in question. The comment is correct that the 1,000 milligrams per kilogram (mg/kg) dose was not used. However, the Commissioner finds that there is sufficient question raised by some aspects of these data, especially with respect to possible testicular damage, to justify the Panel's request for further feeding studies to finally resolve the issue of the long-term toxic effects of this drug.

60. A comment, referring to a chart of the relationship of product classes to ingredients (39 FR 33115), requested that cloflucarban be classified as "NA" (not applicable) rather than in Category II for use as a patient preoperative skin preparation, skin antiseptic, skin wound protectant and surgical hand scrub. The request is based on the fact that the Panel so categorized a number of other ingredients that have never been included in commercially marketed products in a given category or that cannot feasibly be used in a product.

The Commissioner advises that the designation "NA" (not applicable) means that the ingredient is considered outside the purview of the monograph. All ingredients beyond the purview of the monograph are considered to be in Category II (no general recognition of safety or effectiveness), and may not be marketed unless there exists an approved new drug application or an amendment to the applicable OTC drug monograph. To avoid any further confusion or misunderstanding on this issue, all NA (not applicable) designations for all ingredients and all product classes will be changed to Category II in the discussion below.

G. COMMENT ON HEXACHLOROPHENE

61. One comment discussed in great detail the Panel's findings and conclusion with respect to hexachlorophene, and stated that "It is our belief that there is documented efficacy for hexachlorophene (HCP) for indicated claims and there is no evidence of lack of safety in infants over 1,450 grams as well as adults, including extreme exposure conditions such as ingestion and burns."

The Commissioner has reviewed the arguments and data presented in the comment and finds no convincing basis for changing its classification as a prescription drug, as set forth in the FEDERAL REGISTER of September 27, 1972 (37 FR 20160), and contained in the regulations in § 250.250 (21 CFR 250.250).

H. COMMENTS ON IODINE AND IODOPHORS

62. A comment questioned the placement of elemental iodine in Category II for safety on the basis of irritancy and delay in wound healing. The comment stated that such products have been proven effective and contended that they have been marketed for many years without a serious problem of delay in wound healing.

The Commissioner has little doubt about elemental iodine's broad spectrum microbiocidal activity. The Commissioner is also aware of the 136-year marketing history of elemental iodine for use on skin and mucous membranes. The issue before the Commissioner is therefore limited to the Panel's view of the safety of iodine's use as a "first-aid" product for treatment of minor superficial wounds. The Panel, in weighing the issues of irritation and delay in wound healing, concluded that the benefits to be derived from iodine's use were outweighed by its known irritancy and the consequent possibility that its use delays wound healing.

The Commissioner does not dispute this finding with regard to effects on occluded areas treated with elemental iodine. The Panel stated that iodine is irritating to broken skin and delays wound healing, especially when occlusive dressings are applied. However, the Commissioner finds that insufficient information was cited by the Panel to sustain their risk-benefit decision with respect to minor, superficial wounds that are not occluded or that are only slightly bandaged. Without such data, the Commissioner cannot conclude at this time that elemental iodine should be classified in Category II or, instead, in Category I with appropriate label warnings against use in situations where the irritancy of the ingredient may inhibit wound healing. For this reason, and because questions remain with regard to the minimally effective dose (use dilution), and the effect of organic load and pH (acidity) on effectiveness, the Commissioner has placed iodine tincture in Category III for use as a skin antiseptic, skin wound cleanser, and skin wound protectant, with testing guidelines for how these questions can be resolved.

63. A comment criticized the statement of the Panel on the toxic effects said to be associated with the use of iodophors in body cavities and large wounds. The criticism was that the Panel had not distinguished between iodophors complexed with a surfactant and those complexed without a surfactant, and that toxic effects can be experienced from iodophors complexed with a surfactant which would not be associated with iodophors complexed with a nonsurfactant.

The Commissioner recognizes that different complexing agents are used with different iodophors; some are surfactants while the povidone (polyvinyl pyrrolidone) portion of the povidone-iodine complex was the only nonsurfactant considered by the Panel. The Commissioner recognizes that insufficient data have been accumulated on the toxicity of complexing agents for iodophors. As noted in paragraph 71 below, the Commissioner is concerned about the problems associated with povidone-iodine when it is placed in deep wounds or body cavities because the larger sized molecules of the povidone portions of the complex cannot be excreted by the kidney, nor is their toxicity known if the molecules are retained by the body's reticuloendothelial system. The Commissioner wishes to confirm that this particular effect does not occur with surfactant-complexed iodophors, such as poloxamer-iodine. However, the Commissioner notes that the toxicity that may be associated with the use of iodine/surfactant complexed formulations has not been well characterized. The Commissioner is concerned about the possibility of delay in wound healing if the surfactant complexes were to be used in deep wounds.

64. A comment objected to the Panel's statement that all iodophors are dependent on the release of free iodine as the active agent and that the complexing molecule acts only as a carrier.

The Panel's statement reflects a carefully considered and commonly accepted opinion in the scientific community. As will be discussed in the response to paragraph 69 below, the Commissioner has carefully reviewed the available docu-

mentation concerning this question and concludes that there is no reason to modify the Panel's statement in the Category III discussion below. The Commissioner realizes that this is an evolving scientific area and that future data may shed new light on the nature of iodophors. Thus the submission of compelling evidence in the future will guide the Commissioner's decision on this question.

65. A comment complained that the Panel in its discussion of iodine-containing antimicrobials confused simple soluble iodine with iodophors containing iodine in a complex. The comment stated that the Panel did not recognize a distinction between free iodine and available iodine and that it gave undue emphasis to the kinetics of conversion of available iodine to free iodine in explaining antimicrobial activity.

The comment deals with a semantic distinction and presents no reasons why the suggested change in language would materially affect the Panel's categorization of particular iodine-containing antimicrobials. The Commissioner is unconvinced that modification of the language in the Panel report in the Category III discussion below would serve any useful purpose. Because of the discussions in paragraphs 64 and 69 of this preamble concerning the nature of povidone-iodine (polyvinyl pyrrolidone-iodine or PVP–I) as a complex or compound, the Commissioner concludes that the activity of both available and free iodine is important; additionally, it is necessary to determine the kinetics of conversion of available iodine to active free iodine to finally resolve the issue.

66. A comment pointed out the danger in an iodophor and detergent (surfactant) preparation coming in contact with starch granules during a surgical procedure, and submitted a reprint of a paper dealing with the problem (Goodrich, E. O., J. R. Prine, and J. S. Wilson, "Iodized starch granules as a cause of starch peritonitis," *Surgical Forum*, 35: 372–374, 1974). The paper, which had not been available to the Panel, concluded that surgical gloves lubricated with powdered starch can cause idiopathic pathology in operations. The starch can adsorb iodophors or detergents; the resultant complex can cause serosal adhesion (abnormal union of serous membrane) and other undesirable effects in the body.

The Commissioner concludes that practicing surgeons should be made aware of the danger cited in the comment. Therefore, he will require a warning for povidone-iodine and iodophor-surfactant products employed in the surgical suite that may come in contact with starch preparations such as those used for lubricating surgical gloves. Professional labeling for products containing povidone-iodine complex, should they be classified as Category I and included in the monograph, shall contain the warning, *"Caution:* Do not use this product in the presence of starch-containing products. Starch can adsorb iodophors and the resulting complex can cause serosal adhesions (abnormal union of the serous membrane) and other undesirable effects in the body."

67. A comment asked that the stability of poloxamer-iodine be recognized as lasting for 2 years at ambient temperature.

Based upon the data submitted, a 2-year shelf life for the poloxamer-iodine at ambient temperature is reasonable. Therefore, the Commissioner will require a 2-year expiration date on this ingredient should it be included in the monograph.

68. A comment stated that there had been confusion in the categorization of poloxamer-iodine. Although finally placed in Category III as a skin wound cleanser, this substance had been initially placed in Category I during the Panel's deliberations.

The Commissioner notes that the preliminary Category I categorization was only tentative. The Panel's final categorization of poloxamer-iodine for this product class was not due to serious safety considerations, but to the lack of data on whether poloxamer-iodine delays wound healing.

69. A comment objected to attributing the antimicrobial activity of povidone-iodine to the free iodine released from the product. The comment claimed that providone-iodine was a compound and not a complex, and that it was the molecule as a whole rather than dissociated iodine that was responsible for the antimicrobial activity.

A complex results from the interaction of two individual compounds, which are held together by weak bonds easily broken to yield the original components. The Commissioner has reviewed the arguments set forth by the comment, and concludes that povidone-iodine is properly considered a complex. Povidone-iodine is listed in the National Formulary, edition XIII, and the United States Pharmacopeia, edition XIX, as a complex that gives a positive starch test for the presence of free iodine, which is well known for its antimicrobial property. This iodine can be present in povidone-iodine only as a contaminant or as a dissociant from the complex. The presence of free iodine undercuts the hypothesis that the povidone-iodine molecule alone is responsible for the product's antimicrobial action. By dismissing the free iodine as the active moiety of povidone-iodine, the comment assumes the burden of proving that the free iodine present in these preparations is not responsible for the claimed antimicrobial activity and that the source of the free iodine is not from the dissociation of povidone-iodine. The comment contains no evidence for this. In fact, the comment refers to the active ingredient in povidone-iodine as "povidone-iodine N.F." As noted, both the National Formulary, edition XIII, and the United States Pharmacopeia, edition XIX, describe the ingredient as a complex. Other standard reference sources, such as AMA Drug Evaluations and the Physicians' Desk Reference, also refer to povidone-iodine as a complex. The description in the latter reference is attributed to the cooperation of the manufacturers whose products are described. The weight of current opinion does not conflict with the Panel's description of povidone-iodine as a complex, and the comment presents no evidence to the contrary.

70. A comment asked for deletion of the statement that povidone-iodine is not capable of being included in a soap formulation. The comment said that the statement is inaccurate.

At the time of the Panel's deliberations, the prevailing view was that formulations containing povidone-iodine (polyvinyl pyrrolidone-iodine or PVP–I) could not be successfully combined with other soap ingredients in a soap formulation. However, since publication of the Panel report, the comment suggests that such a formulation has become possible using povidone-iodine. The Commissioner agrees to delete the statement of incompatibility of povidone-iodine in soap formulation.

71. A comment contended that there should be restrictions on the use of povidone-iodine (PVP–I) according to molecular size. Published research cited in the comment indicates that povidone-iodine molecules larger than 35,000 daltons cannot be excreted by the kidneys, can cause nodules to appear in the lymphatic system, and may induce cosmetic deformities in the area of healing skin wounds.

The Panel recognized a relationship between molecular size and nodular lymphatic changes accompanying exposure to providone-iodine, but made no decision on limiting the molecular size causing such pathology. The Commissioner, based on expert opinion and the extensively documented comment, has determined that a molecular weight of 35,000 daltons is the safe upper limit for parenteral exposure to providone-iodine. This calculation assumes that a providone-iodine molecule with this molecular weight would be too large to pass through the kidney.

The Commissioner is also aware of inappropriate use of providone-iodine products in open wounds and in the abdominal cavity during surgery. To promote proper use of providone antimicrobials, therefore, should they be included in the monograph, he proposes to recognize two categories of such products. Products with providone-iodine molecular weights greater than 35,000 daltons will be limited to use on intact skin; those with molecular weights less than 35,000 daltons will be permitted for general use. Appropriate labeling would place each product in its proper category of use. The professional labeling of providone-iodine products containing molecules greater than 35,000 daltons would also include warnings against parenteral use of, and exposure of open surgical wounds or deep wounds to, the product.

72. Comments asked for transfer of povidone-iodine from Category III to Category I for use as a skin wound cleanser, health-care personnel handwash, patient preoperative skin preparation, and surgical hand scrub. The comments contended that povidone-iodine

is less toxic and less irritating than, and just as effective as, tincture of iodine, which received a Category I classification for use as a patient preoperative skin preparation. The comments also argued that many of the concerns stressed by the Panel are not applicable to claims for the particular product classes in this report or are irrelevant due to the size of the povidone-iodine molecule.

The Commissioner has carefully considered whether the problems identified in the Panel report are substantial enough to preclude classification of povidone-iodine in Category I. On the basis of submissions made to the Panel, information in the comments on the Panel's report, and his independent review of all the available data, the Commissioner concludes that there still remains a lack of sufficient data to reclassify povidone-iodine in Category I.

I. COMMENTS ON PARA-CHLORO-META-XYLENOL

73. A comment asked that para-chloro-meta-xylenol (PCMX) be reclassified in Category I for use as a skin antiseptic and skin wound cleanser when formulated in an aqueous alcoholic base containing pine oil and vegetable soap diluted before use with water to a concentration of not more than 0.5 percent.

The Commissioner concludes that the data submitted in the comment do not provide sufficient additional information by which to establish the safety and effectiveness of products containing PCMX. The comment relies on the long marketing history of the product as support for both safety and effectiveness. Much of the early published data were resubmitted. As the comment noted, some of the early studies are well done for the time. However, they are not sufficient to satisfy the testing guidelines set forth below.

One of the Commissioner's continuing concerns is the absorption of topically applied products, particularly if these products are used repeatedly by consumers over many years. Very little data were submitted concerning absorption of PCMX. Studies to establish the safety of topically applied PCMX should be available before a determination is made about the final classification of the ingredient.

J. COMMENTS ON PHENOL

74. Several comments requested transfer of phenol at less than 1.5 percent from Category III into Category I for all product categories. The comments stated that phenol at less than 1.5 percent has been placed in Category I by the ongoing OTC Oral Cavity and OTC Topical Analgesic Drug Panels, and contended that it is contradictory for different Panels to place the same ingredient in different categories.

That one Panel places a substance in a given category does not require another Panel to place it in that category for a different use on a different part of the body. Additionally, the Commissioner notes that he has not yet received the final report of either of the two Panels referred to in the comment. When the Commissioner has those reports, he will be able to compare the scientific basis and reasoning for the differences in the Panel recommendations on phenol. If these differences are based on different claimed uses or upon intended uses in different body sites sufficient to justify different recommendations, he will most likely not modify those recommendations.

The Panel, in its review of phenol at less than 1.5 percent in aqueous or alcoholic solution (39 FR 33133), noted potential safety issues, and the Commissioner agrees that these must be resolved before phenol at less than 1.5 percent concentration can be reclassified in Category I for all the product classes reviewed by this Panel.

K. COMMENTS ON POLOXAMER 188

75. A comment was received requesting that pluronic F-68 (poloxamer 188) be placed in Category I as a safe and effective skin wound cleanser.

Poloxamer 188 is a member of a family of block copolymers called pluronic polyols. It contains 80 percent ethylene oxide by weight and has a molecular weight of 8,350. There is a long history of its use as a nonionic surfactant detergent in a variety of preparations, including certain intravenous products. It is generally regarded as nontoxic and is rapidly excreted intact by the body. Although it has no antimicrobial activity, it has been employed widely as a detergent and fat emulsifier and is recognized as nonirritating and efficient for minor wound cleasing when employed in aqueous solutions.

After reviewing the comment and the submitted supporting data, the Commissioner places poloxamer 188 in aqueous solutions in Category I as a skin wound cleanser. The use concentration of poloxamer 188 as a skin wound cleanser is limited to 20 to 40 percent aqueous solutions since this is the range of concentrations most studied and reported on. Since this compound has no antimicrobial activity, it cannot make those claims permitted for an active antimicrobial ingredient in a skin wound cleanser, e.g., "contains antibacterial ingredient", "contains antimicrobial ingredient", nor can it be generally recognized as safe and effective for the other product classes. This classification does not, of course, prohibit its use as an inactive ingredient or pharmaceutical aid for its detergent and surfactant properties.

L. COMMENTS ON TRICLOCARBAN

76. A comment indicated a belief that data would be forthcoming that would resolve the issue of the degree of absorption of triclocarban through the skin such that triclocarban could be placed in Category I as an ingredient in an antimicrobial soap.

The Commissioner has received recent data from a study on the percutaneous penetration (absorption) and metabolic decomposition of triclocarban in man. These data were determined after total body showering with a liquid soap containing 2 percent radioactively labeled triclocarban (approximately 7 gm). The amount of triclocarban absorbed from topical application in one shower closely corresponds with the amount yielded by the calculations of the Panel. The study thus confirmed a number of key assumptions relating to absorption of this ingredient that the Panel made in the absence of data. The Commissioner concludes that the Panel accurately computed the safety factor for one shower per day to be 1,000-fold and for two showers per day to be 500-fold. These far exceed the 100-fold minimum safety factor suggested by the Panel.

Although the safety questions the Panel raised about the degree of absorption in humans have been resolved to his satisfaction, the Commissioner is unable to modify the tentative final monograph to include triclocarban in Category I for use as an OTC antimicrobial soap. This is due to a question that has arisen regarding the validity of one of the basic long-term toxicity studies performed on this drug, a 2-year oral chronic toxicity animal study. The Commissioner has reached the conclusion, in another forum, that though the study design is adequate this particular study is invalid. The Commissioner will therefore retain triclocarban in Category III as an antimicrobial bar soap at a concentration of 1.5 percent until such time as this study is duplicated. Upon reviewing all evidence surrounding the study in question, the Commissioner has also reached the conclusion that omission of these data is not sufficient justification for classifying triclocarban in Category II as an antimicrobial bar soap at this time. Since the bulk of the data are based upon absorption characteristics of bar soap formulations, Category III status for antimicrobial soaps will be restricted to bar soaps. Because no data were presented to the Panel during its deliberations or to the Commissioner during the comment period concerning the safety and effectiveness of triclocarban for use in other types of products, triclocarban remains in Category II for all product categories except antimicrobial bar soaps, health-care personnel handwashes (bar soaps only), and skin wound cleansers (bar soaps only).

77. A comment stated that determination of substantivity of triclocarban (the degree to which it binds to the cells of the outer layer of the skin) is irrelevant to normal use of bar soaps and is only of academic interest, and that the only important concern is the determination of blood levels of the active ingredient.

The comment is apparently arguing that, with knowledge of blood levels of triclocarban, determinations of the amount and persistence of triclocarban on the skin is not needed. The Commissioner agrees with this contention insofar as it relates to antimicrobial soaps. However, adequate knowledge for a determination of the safety and effectiveness of triclocarban for the other product classes within the purview of this document includes data on substantivity.

Greater substantivity may increase effectiveness by permitting the ingredient to remain at the site of action for a longer period of time. In addition, substantivity affects the duration and maximum concentration of the ingredient in the blood. The Commissioner therefore concludes that knowledge of substantivity is a necessary part of the toxicologic profile of all topical antimicrobial product classes except antimicrobial soaps. Whether an ingredient is adsorbed onto the skin, held for a long time, and, when accumulated to the maximum extent possible, causes skin pathology, are important factors in evaluating the safety of the ingredient.

78. A comment stated, on the basis of personal experience, that, after stopping use of triclocarban soap and using another kind of soap, skin blotches cleared up.

The report is testimonial and is not supported by independent verification from a physician. Although the incident cited might be attributable to contact sensitivity to triclocarban, it cannot be considered a definitive demonstration of the phenomenon because the possibility of sensitivity to other ingredients in the soap was not eliminated.

79. A comment stated that the Panel relied solely upon unpublished and nonpublic data to support its conclusion that triclocarban and cloflucarban should be limited to a 1.5 percent concentration in soaps. The comment objected to sole reliance on unpublished data, contending that this makes it impossible for interested parties and the public to make meaningful comments on the Panel's conclusions.

The comment disregards the fact that virtually all data relied upon by the Panel were placed in the public record in the office of the Hearing Clerk, Food and Drug Administration, 30 days after publication of the report and proposed monograph. In fact, the Commissioner extended the period for public review and comment specifically to permit greater time to analyze any data that had not been publicly available before the report was published.

80. Comments contended that the scientific literature does not show cloflucarban and triclocarban to be photosensitizers. The comments objected to the language of the Panel discussion that implied that these antimicrobials could be photosensitizers. The comment noted that the paper of Masuda, et al., listed in the references under cloflucarban, did not record any evidence for photopatch-test positive reaction with triclocarban or cloflucarban among 140 patients tested.

The Commissioner agrees that the literature cited by the Panel and the comment contains no data that triclocarban and cloflucarban cause photosensitization. Consequently, the Commissioner will not require testing of either ingredient for photosensitivity.

M. COMMENTS ON TRICLOSAN

81. A comment contended that a double standard was applied to place triclosan in Category II but benzalkonium chloride in Category III for use as a health-care personnel handwash, patient preoperative skin preparation and surgical hand scrub. The comment argued that application of the same standard to both compounds would place them in the same category, and requested reclassification of triclosan into Category III.

The Panel clearly indicated in its report that triclosan was placed in Category II for the uses mentioned on the basis of its known lack of activity against *Pseudomonas* species of microorganisms. In fact, triclosan is used in isolation medium to bring about the selective growth of *Pseudomonas* species. The Panel action was based on its opinion that triclosan presents a greater selective ecological pressure for growth of *Pseudomonas* in the closed hospital environment than do the quaternary ammonium compounds. Today the *Pseudomonas* infections constitute the greatest bacteriological threat of infection in the hospital environment. The questions and risk associated with the increased use of triclosan in multiple daily-use products have continued to increase since the publication of the Panel's report and resolution of these issues becomes even more important. The Commissioner concludes that the Panel's classification of triclosan in relation to benzalkonium chloride was based on a relevant difference between the two ingredients and was entirely proper.

82. A comment asked that the use of triclosan be allowed up to a 2 percent concentration to ensure effectiveness and claimed that such a concentration is well within appropriate safety limits for toxicity. The comment included calculations on safety factors that indicated a range of from 821- to 5,000-fold over the concentrations requested.

The Commissioner has reviewed the data and the Panel discussion pertinent to the comments. Because of the possibility that increasing use of triclosan in consumer products may raise blood levels to an unacceptable degree, the Commissioner will restrict the concentration of triclosan to 1 percent for the Category III conditions. The Commissioner wishes to emphasize that he is in accord with the Panel's view that no more than the minimal effective concentration should be used in these products, as determined by the results of the tests in the testing guidelines.

83. A comment asked for reclassification of triclosan from Category III to Category I for use in skin antiseptic, skin wound cleanser, and skin wound protectant products. Another comment requested that triclosan be placed in Category I as an antimicrobial bar soap in view of additional data submitted with the comment. Other comments expressed no dissatisfaction with the Category III classification for the "first aid" product classes and indicated a willingness to perform the testing required to justify Category I classification for such indications.

The Commissioner notes that until the summer of 1976 no data were available that would justify reclassifying triclosan from Category III to Category I for use in skin antiseptic, skin wound cleanser, and skin wound protectant products. Even though additional animal data have been reported since the Panel's report, questions have recently arisen regarding the validity of key animal studies with triclosan. In view of these questions and in view of the apparent ever widening distribution of triclosan in consumer products, the final resolution of risk to benefit for triclosan cannot be made at this time. Accordingly, triclosan is retained in Category III for these indications.

84. Comments pointed out that a report, cited by the Panel, of hyperpigmentation associated with the use of a triclosan-containing soap should not be interpreted to mean that triclosan caused the hyperpigmentation. The case referred to by the Panel showed development of hyperpigmentation on both the nonexposed control hand and on the hand washed with triclosan soap. No other test subjects showed development of hyperpigmentation.

The comment is accurate. Therefore, the Commissioner is deleting from the Category III discussion of triclosan any reference to its being known to cause skin hyperpigmentation.

N. INGREDIENTS DEFERRED TO OTHER PANELS

85. A number of comments requested that 3 percent hydrogen peroxide solution, and methyl, ethyl and isopropyl alcohol, be included in the antimicrobial monograph because of their long and widespread use as antimicrobials. The comment stated that otherwise, these products would not be available for use as antimicrobials. Another comment requested that gentian violet 1 percent and 2 percent solutions, thimerosal tincture, and mercurochrome be included in the OTC antimicrobial monograph as Category I skin antiseptics.

The Commissioner recognizes that these ingredients have a lengthy history of use and that data on their toxicity and antimicrobial activity are readily available. These preparations have, however, been assigned for review to the OTC Miscellaneous External Drug Products Panel. Relevant data may be submitted to that Panel in the form required by 21 CFR 330.10(a)(2) and addressed to: Food and Drug Administration, Division of OTC Drug Evaluation, Rm. 16–85, HFD–510, 5600 Fishers Lane, Rockville, Md. 20857. In accordance with the policy announced by the Commissioner in the preamble to the Procedures for Classification of OTC Drugs published in the FEDERAL REGISTER of May 11, 1972 (39 FR 9464), no action will be taken to remove them from the marketplace pending completion of their review by the External Miscellaneous Panel and publication of a final monograph for them.

O. COMMENTS ON TESTING REQUIREMENTS AND GUIDELINES

86. Several comments objected to the requirement for testing both the individual antimicrobial ingredient and the finished formulation, contending that

such testing is duplicative and only of academic interest.

While (as noted in paragraph 7 above) the amount of such testing will be limited to certain products, the Commissioner disagrees that testing both the ingredient and the product is duplicative. For certain product classes specific product formulations may render an ingredient ineffective or unsafe. If the ingredient and the formulation have not both been tested, it in not possible to determine if there is a difference in the safety and effectiveness of the active ingredient as compared with the finished product. Once an ingredient has been classified as generally recognized as safe and effective, no further data on finished formulations need be submitted to the agency. However, such data should be on file for inspection.

87. Several comments objected to use of the phenol coefficient determination as a requirement in the testing guidelines because phenol coefficients have the most value in comparing the relative bactericidal activity of modified phenolic compounds with phenol. They further argued that the phenol coefficient is not a valid criterion for testing effectiveness of bacteriostatic preparations and is not even completely adequate for bactericidal preparations because many effective nonphenolic antimicrobials may, because of their chemical structure, not have a high phenol coefficient.

The Commissioner agrees that the phenol coefficient is not always the best way of judging the value of an antimicrobial. The textbook *Basic Bacteriology* by C. Lamanna, M. F. Mallette, and L. Zimmerman (1973) states that "it is probable that the search for a single test, numerical value, or coefficient (i.e., phenol coefficient) to express the relative worth of disinfectants will remain a will-o-the-wisp as a scientific venture" (p. 1044).

The phenol coefficient has the merit of expressing the degree of disinfection by a number, thus permitting ready comparison among antimicrobials. This exercise, however, is only as meaningful as the numbers that are used. Bacteriologists agree on the weakness of the phenol coefficient, although some are willing to rely on it for want of a better method.

The Commissioner concludes that, in light of the diversity of opinion and the strong feelings throughout the scientific community on the value of the phenol coefficient, the testing guidelines should be modified to make it clear that this method is optional. Therefore, the testing requirements for effectiveness, which call for a phenol coefficient determination, will be deleted, and paragraph f. will be modified by adding the term "and phenol coefficient" after "Sykes-Kelsey." See paragraph (4) of the testing requirements later in this document.

These changes meet the criticisms in the comments and are fully consistent with the intent of the Panel that the activity of an antimicrobial ingredient be fully characterized. The phenol coefficient determination will be one of several standard tests permitted, depending on the circumstances.

88. A comment requested clarification of the meaning of subchronic and chronic exposure tests of a product on interest and abraded skin, as discussed in the Panel's safety testing requirements (39 FR 33135).

Although the Panel did not specifically define chronic and subchronic testing, these terms have a generally accepted meaning in the scientific community. Subchronic testing means repeated application or dosing of the test material for up to 90 days. Chronic testing means repeated exposure for more than 90 days.

89. A comment argued that investigation of the degree of absorption of an ingredient from intact and abraded skin and mucous membranes in subchronic animal testing (less than 90 days) is superfluous once results of chronic human studies are obtained.

Absorption tests are necessary for the determination of blood levels of antimicrobials in chronic use. The Commissioner is primarily concerned with the time it takes for blood levels to plateau. It is possible to extrapolate chronic absorption data to subchronic conditions. Therefore, when there is no sacrifice in the quality of the data, the Commissioner will not require subchronic absorption testing when adequate chronic testing has been performed. However, blood levels after acute or short-term use will also have to be determined.

90. A comment stated that it is improper to require carcinogenicity, mutagenicity, teratogenicity or other reproduction studies wih finished antimicrobial products. The comment did not object to such testing of the active ingredients.

The Commissioner agrees that it is not necessary to conduct such studies with the marketed product where adequate data are available on the active ingredients alone.

91. A comment objected to the Panel's calculation of the safety factor for triclocarban. The calculation assumed 100 percent retention and absorption, whereas data for triclocarban show less than 100 percent retention and absorption, the coment said. The comment pressed concern that the Panel's assumption would be interpreted as a requirement for making calculations in disregard of real life situations for particular compounds, such as triclocarban, for which it can be demonstrated that retention and absorption are less than 100 percent.

The Panel clearly stated that due to the lack of objective data its calculations were based on assumptions intended to illustrate the kind of calculation required in evaluating retention and absorption. The Panel statement did not preclude use of objective data to replace the assumption of 100 percent retention and absorption for a specific ingredient or product. Subsequent to publication of the Panel report, a study was carried out which measured percutaneous penetration (absorption) and metabolic decomposition of radioactively labeled triclocarban in humans (see paragraph 76). The Panel's assumptions relating to absorption and retention of 100 percent of the available antimicrobial on the skin were not confirmed. However, the quantity of triclorcarban absorbed was remarkably close to the calculations based on those assumptions. Accordingly, for the other ingredients reviewed, but not yet tested for the degree of absorption in the same manner as triclocarban, the Commissioner agrees that when reliable data are available for retention and absorption of that particular ingredient or product, the safety factor calculation ought not be made on the basis of an assumption of 100 percent retention and absorption.

92. A number of comments objected to the requirement in the guidelines for obtaining the LD_{100} and the LD_0 in addition to the LD_{50}.

The Panel's guidelines for testing call for "The LD_{50}, highest dose killing no animals and lowest dose killing all the test animals by oral and topical routes, if possible" (39 FR 33135). The LD_{100} and LD_0 can be estimated from the dose-response curve necessary to determine the LD_{50}. Since the guidelines impose no requirement beyond obtaining the LD_{50}, other than performing additional calculations, the Commissioner concludes that no change is appropriate.

93. Several comments objected to the requirement that the fungicidal and viricidal activity of antimicrobial soaps be tested even when the products make no such claims. The comments stated that testing of products for effectiveness against microorganisms for which they are not labeled should not be required.

In characterizing the activity of an active ingredient for antimicrobial soaps, the Panel limited labeling claims to "reduction of odor." The Commissioner believes that a deodorancy claim must be substantiated by testing to characterize the antimicrobial activity of the active ingredient because odor is generally caused by gram-positive or gram-negative bacteria. Since odor is not usually caused by fungus or virus conditions, testing of the active ingredient for fungicidal and viricidal activity will not be required. Of course, there must be no claims, either direct or by implication, that a product has activity against organisms for which it has not been tested.

The Commissioner notes that this testing requirement is limited to effectiveness. If there is a reasonable scientific indication that the activity of an ingredient will affect the microbial flora, resulting in a possibly harmful rise in the fungus or virus level, then testing for fungicidal and viricdal activity would be required.

94. A comment objected to the Panel's recommendation of the Sykes-Kelsey procedure for antimicrobial effectiveness testing because it measures only the effectiveness of hard surface disinfectants.

The Sykes-Kelsey test is designed to determine the effect of organic material, i.e., killed yeast cells on the antimicrobial activity of an ingredient or formu-

lation. The test is not limited to testing products for use on hard surfaces, and is equally applicable to testing products for topical use on humans. Moreover, the Panel did not recommend that only the Sykes-Kelsey procedure be used, but suggested other procedures "where applicable."

95. A comment referred to the safety testing guidelines and stated that "skin pigmentation is a routine observation made as part of all Repeated Insult Patch Tests, and separate tests seem superfluous."

The Panel's test requires observation for skin pigmentation; it does not prohibit observation for that phenomenon concomitant with patch tests for other purposes, and the testing guidelines below are modified to make this clear.

96. A comment requested clarification of the age group required be tested for phototoxicity and photoallergy.

The appropriate age group is males over 40 years of age. The reported incidence of photoallergy is highest in this group.

97. A comment noted that the Panel's testing requirements called for determining the primary irritation potential of the active ingredient both alone and in its final product formulation on the skin, with special attention devoted to eyes, mucous membranes, and genitalia. The comment did not object to testing the active ingredient alone on skin and eyes because employees engaged in the manufacture of antimicrobial ingredients would have their skin and eyes exposed to the active ingredient in its raw form. However, the comment contended that since mucous membranes and genitalia would be exposed to the active ingredient only in the final product formulation, and not in its raw form, testing of those areas of the body with the active ingredient alone is not necessary.

The importance of accurately determining the safety of these products and their ingredients makes it necessary that both the active ingredient and the finished product be tested for primary irritation potential. The Panel recognized the merit of carrying out this primary irritation potential test in animal models first, which would permit the elimination of obviously irritating materials without the need for further testing in humans. Because the use of antimicrobial bar soaps exposes the entire human body to the active ingredients they contain, it is important to test each active ingredient, as well as the finished product, on the most sensitive tissues of the body, such as the mucous membranes and genitalia. The purpose of testing the active ingredient alone is not to duplicate anticipated conditions of actual use, but to reveal any drastic irritation potential of the ingredient that might be masked in the finished product.

98. One comment stated that it is not necessary to test the effect of the active ingredient alone on wound healing, and that substantivity studies on the active ingredient are not appropriate. Only the final product should be tested, the comment contended.

The Commissioner disagrees. The purpose of the testing required by the Panel is to identify the toxicologic profile of the active ingredient and to determine the possible effects on its activity of the formulation of which it is a part. This information is necessary to the Commissioner's application of the statutory criteria governing drug safety and effectiveness. As explained in the preceding comment, testing of the active ingredient alone, in relation to delay in wound healing or any other significant adverse potential, is necessary to eliminate the possibility that its effects are concealed by other ingredients in the formulation of the finished product. Substantivity testing (testing to determine retention of the ingredient in the horny layer of the skin) is also a necessary part of the toxicologic profile. It should be carried out with the formulated product and, for the reasons indicated, with the active ingredient in an innocuous vehicle.

99. A comment stated that it is not necessary to require in vivo controlled human studies with a skin antiseptic such as povidone-iodine in cases where the product claims are limited to degerming, microbiocidal, bacterostatic and bactericidal properties. These claims, the comment contended, can be adequately demonstrated by in vitro testing, especially when the product is not for use as a skin antiseptic, but only in conjunction with medical devices, such as catheterization products, to reduce the potential that skin organisms will be transferred by the device to the body parts in contact with it.

The comment refers to preparations associated with procedures intended for lay use either by patients at home or by paramedical personnel on the advice of physicians. The uses are for special or limited circumstances, including needs of colostomy hygiene and urinary catheterization by individuals at home who have suffered loss of certain bodily functions. When such products are used, they are applied to the site of insertion into the body and frequently to the device at the site it enters the body. Because of the serious nature of infections at these sites, the Commissioner believes that antimicrobial ingredients to be used for such purposes must be both safe and effective and must, therefore, meet the requirements of patient preoperative skin preparations set forth in the definition of this product class and in the testing guidelines. Although such testing would necessarily include clinical studies, the Commissioner is prepared to accept suggested modifications to the testing guidelines because of the ethical considerations relating to the control aspect of the studies.

In addition, the Commissioner notes that no submissions were received during the OTC review for the indications described above. Consequently, specialized labeling for such products will only be permitted through an amendment to the OTC topical antimicrobial monograph or through approval of a new drug application.

100. A comment, referring to the Panel's recommended testing for solation of gram-negative and other organisms from the skin," suggested deletion of triclosan containing agar as a selective medium for isolation of *Pseudomonas* because work has shown that triclosan has limited effectiveness for this purpose.

Triclosan-containing agar medium is not the only bacteriologically selective medium of limited effectiveness. It is currently accepted, available, and marketed as a selective medium for use in diagnostic and other laboratories. Until the consensus of expert opinion on the usefulness of triclosan agar changes, it would be inappropriate for the Commissioner not to permit the use of triclosan agar medium for isolation of *Pseudomonas* species.

101. A comment suggested that there is no need to demonstrate effectiveness of antiseptics on superficial skin wounds against viruses or the *Neisserea* species of bacteria, both of which are virulent microorganisms that cause serious diseases, e.g., menningitis and gonorrhea, and neither of which is found in the normal environment of the skin or in a superficial wound.

The testing required for proof of effectiveness against microorganisms, which appears in the testing guidelines below, is in vitro and is intended to characterize the activity of the antimicrobial ingredient and product in the normal environment and not under every possible circumstance. Therefore, though the Commissioner expects representatives of the various microbial groups to be tested in vitro, use of the claim "skin antiseptic" will be permitted without demonstration of antimicrobial action against viruses and *Neisserea* species. However, the Commissioner cautions that such in vitro testing will not be the sole determinant of effectiveness and that clinical testing in accordance with the testing guidelines will be required to place an ingredient in Category I. The Commissioner also notes that because of the limited spectrum of antimocrobial activity for which testing must be done, the labeling under the monographs for skin antiseptics (21 CFR 333.90), skin wound cleansers (21 CFR 333.92), and skin wound protectants (21 CFR 333.94) is modified to include a warning that the product is not to be employed in wounds as a prophylactic against rabies infection in the case of animal bites unless proof for this use is provided to the agency. The warning states: "This product is not for use on wild or domestic animal bites. If you have an animal bite, consult your physician immediately".

102. Comments referring to both the product class definitions and the Panel's testing guidelines discussed the difficulties of in vivo testing in humans for the effectiveness of skin antiseptics and skin wound protectants against experimentally induced wounds (39 FR 33108, 33136). The comments raised questions about the ethics of such experimentation and noted constraints imposed on the scientific value of such tests by the current state of the art. The comment noted

that the Panel did not specify what pathogens should be used to induce the experimental infections, and argued that data on effectiveness against one pathogen are of limited predictive value with respect to effectiveness against other pathogens. For this reason, the comment suggested that there should be a requirement only for in vitro tests. This would make it practical to test a wide spectrum of pathogens and would avoid ethical questions about experimentally infecting wounds in humans.

The Commissioner agrees that the comment raises serious questions. However, the Panel's statements do not imply a rigid limitation to testing in experimentally infected human wounds. Rather, they recommend that antimicrobial ingredients be tested for their effectiveness in the normal wound healing process in the presence of those organisms (including pathogens) encountered in the normal environment. The kinds of tests to be performed, which are determined by the scope of the claims made for the products, are set forth in the testing guidelines below. Since the subjects of studies will be volunteers who have given informed consent and since there is no intent to expose volunteers to known virulent microorganisms, the Commissioner concludes that the testing procedure described in the testing guidelines are ethical and should be retained.

There are three kinds of tests that can be considered: (1) Controlled study of experimental wounds in humans conducted in accordance with accepted ethical standards; (2) controlled study of wounds in experimental animals; (3) in vitro tests employing human tissue culture models. Which test is employed will be determined both by the state of the art and by the nature of the claims made for the product. However, under the present testing guidelines, delay of wound healing by antimicrobial ingredients will be considered a separate issue from determination of effectiveness against specific pathogens that affect healing.

The Commissioner has received recent information on the use of hygrometry to assess wound repair and has included it in the testing guidelines. The Commissioner encourages further research and development of wound models employing human tissue cultures. Potentially, such research should lead to scientifically valid substitutes for the experimental wounding of humans and thus eliminate the need for testing in human volunteers.

103. A comment suggested that in testing the effectiveness of health-care personnel handwash products, the requirements for dipping the hands of volunteers into a liquid culture of microorganisms be replaced by one for spreading a know aliquot (sample) of bacterial culture on the hands. The comment said that this is a more scientific procedure because it assures better control of the number of microorganisms deposited on the skin.

The Commissioner concludes based on the submitted data that either procedure is acceptable. Spreading a known aliquot of culture may give greater certainty about the number of organisms deposited on the hands, but it may not assure a uniform distribution of microorganisms over the entire area of the hand unless care is taken.

104. A comment stated that it is unreasonable to require testing of health-care personnel handwash products by having "an individual wash for 6 hours which is the total time required for 100 washes in a day required by the Panel."

The comment misinterprets the Panel's requirement. The Panel merely reported that a product should be safe enough to be used repeatedly, "perhaps 100 times a day." It did not suggest that 100 washes a day is the norm for testing. Rather, it recommended 25 washes in succession, with not less than a 5-minute interval between each wash. The Commissioner intends to retain this testing procedure.

105. Several comments suggested substituting the micro-organism, *Escherichia coli* for *Serratia marcescens* in tests for the effectiveness of health-care personel handwash products. The comments pointed to a potential risk of human infection from *Serratia marcescens*.

The Panel was aware of reports of *Serratia marcescens* infections. However, there is a long history of safe use of segmented laboratory-cultured strains of this species. *Serratia marcescens* is superior to other organisms for use in tests because it is easily isolated and grown in the laboratory and because its characteristic pigmentation makes for reliable identification. The Commissioner concludes that the microorganism *Serratia marcescens* should continue to be used as a marker species in the testing guidelines for health-care personnel handwashes as well as for certain other categories of antimicrobial products.

106. A comment contended that there is no justification for the Panel's recommendation that health-care personnel handwash products be tested in a manner that exposes test subjects to the risk of infection from bacteria not normally part of the microbial flora of the skin.

The Panel did not suggest that virulent microorganisms be used to contaminate the hands and forearms of test subjects. Marker strains of bacteria to be used in this type of test should be avirulent, as will be noted in the testing guidelines.

107. A comment asked that the millipore filter procedure be permitted for isolation of microorganisms from wash water used in testing the effectiveness of health-care personnel handwash products.

The Commissioner agrees. The millipore filter technique is well established, the necessary equipment is readily available, and modern academic courses of instruction in microbiological techniques teach it. The millipore filter technique will be included as an option in the testing guidelines.

108. A comment objected to excluding persons taking oral contraceptives from participating in the glove juice tests required to prove the effectiveness of surgical hand scrubs. The comment cited an unpublished reference that oral contraceptives have a stabilizing rather than an adverse effect on the microbial flora of the skin.

These data have not been subject to independent verification. Even if they are correct, use of persons taking oral contraceptives adds another variable that can easily be eliminated because there is an adequate pool of subjects who do not take such drugs. The Commissioner therefore concludes that the Panel's recommendation should be retained.

109. A comment asked that in the case of nonpowdered gloves, and when the the hands are wet, the glove juice test should proceed without a prewash or wetting of the gloves.

The requirements of the glove juice test were carefully considered by the Panel to eliminate certain variables. The prewash removes superficial transient microbiological flora prior to the test. The gloves are required to be wet when the gloves are donned to assure a better controlled test. Because of the importance of these factors to the reliability of the results of the glove juice test, the Commissioner concludes that the testing protocol should remain as recommended by the Panel.

110. A comment asked that, in the glove juice test, tap water rather than sterile distilled water be permitted in baseline period and sampling fluids.

The Commissioner does not agree that tap water is an acceptable replacement for sterile distilled water in the glove juice test. Use of sterile distilled water helps assure control of variables among different laboratories. Any institution with the technical sophistication required to run the glove juice test would have a readily available source of sterile distilled water.

111. A comment suggested that lecithin replace serum in the bacteriological recovery medium used in the glove juice test.

The use of either serum or lecithin will be permitted. In either case, however, the neutralizer employed in the bacteriological medium must be shown not to be toxic to the cells being isolated and to neutralize the biological activity of the antimicrobial under test.

112. Several comments asked that the baseline handcount requirement in the glove juice test protocol be modified because most human subjects do not give hand counts of bacteria in the narrow range of $\log_{10}$ 6.176 to 6.602 required for eligibility of volunteers by the Panel's test protocols. Data were presented to show that the glove juice test gives uniform results with subjects who have hand counts of bacteria in the broader range of $\log_{10}$ 4.0 to 7.0.

The Commissioner has reviewed the data and does not find them sufficient to assure that results will be uniform if hand counts in the range suggested are used. The requirement will therefore not be modified at this time without further independent corroboration. When such supporting evidence becomes available, a change in the requirement will be considered.

113. A comment asked for a reduction in the total number of time intervals for taking samples for bacterial counts in the glove juice test. Instead of taking samples at the 1-minute, and the 1-, 2-, 3-, 4-, 5- and 6-hour intervals, samples would be taken at the 1-minute, and the 1-, 3- and 6-hour intervals. The comment stated that this would be more economical and would not reduce the reliability of the result.

The time intervals were chosen on the basis of advice from expert consultants in biostatistics, who advised that the sampling times are required to establish the rate of re-growth of the bacterial flora after the gloves are donned. The comment does not substantiate its conclusion that fewer sampling intervals will not decrease the reliability of the result. The protocol accordingly will not be changed.

114. A comment asked that the requirement for a 1-minute massage of the gloved hand be eliminated from the glove juice test because the bacterial count can vary with the vigor of the massage, independent of its duration.

Although the bacterial count may vary with the vigor of massage, without massage there will be an inherent variation among samples due to differences in the strength of adhesion of various bacteria to the skin surface. The Commissioner concludes that careful execution of the procedure will minimize differences in the vigor with which hands are massaged, and that completely abandoning the procedure would merely introduce another variable that could not be dealt with by any technique, other than massage, known to the Commissioner.

115. A comment stated that a 1-day prohibition on hand washing is an excessive demand to place on persons volunteering as subjects for glove juice tests (39 FR 33138).

The Panel stated that "Subjects should not wash prior to the counting procedure on the day of the test." The prohibition recommended by the Panel would extend from awakening to the point at which the counting takes place. Since counting can be scheduled at any time, it is open to the investigators to schedule it early in the day, thus minimizing inconvenience to the participants. This is clarified in the testing procedures included in this document.

116. A comment characterized the proposed glove juice test as so expensive that only the largest manufacturers can afford it. The testing requirements were said to be unnecessary and a waste of time, resources, and money and that insistence upon the testing would make it desirable, if not necessary, for the government to take over the costs involved.

The criticism ignores the general acceptance by industry, the scientific community, and the medical profession of the need for the glove juice test. For a given ingredient, the glove juice test is a one-time requirement for entrance into the marketplace as a surgical hand scrub, not a recurring cost. The Commissioner realizes that the cost factors involved are of importance to industry. However, public health considerations are an overriding concern. Moreover, the requirement that Category III testing be carried out by each manufacturer has been changed by a regulation published in the FEDERAL REGISTER of April 12, 1977 (42 FR 19137).

P. MISCELLANEOUS COMMENTS

117. A comment suggested that the section of the monograph dealing with the labeling of patient preoperative skin preparations (§ 333.80, redesignated § 333.87 below) is somewhat confusing and should be rewritten to indicate which labeling requirements apply generally to patient preoperative skin preparations and which apply specifically to tincture of iodine.

The Commissioner has reviewed the request and finds it reasonable. This section is rewritten and reorganized into both general and specific labeling requirements.

II. THE COMMISSIONER'S CONCLUSIONS ON THE CATEGORY II RECOMMENDATIONS

The Commissioner's conclusions and restatement of the Panel's recommendations and conclusions for Category II are set forth below. The Commissioner adopts these findings by restating the appropriate sections of the Panel's findings in this document, with modifications for clarity and regulatory accuracy, as well as for new data and information that have come to his attention. Changes based on new data and information are discussed in the preamble. Gratuitous or unsupported statements have been excluded. The Commissioner's agreement with comments suggesting modification of the Panel's findings are incorporated in the Commissioner's restatement of them.

The Commissioner is not restating those parts of the Panel's findings that are not directly relevant to his decision on the content of Category II. Specifically, he has omitted sections of the Panel report relating to preservatives, inactive ingredients, balance of normal flora, effectiveness for erythrasma (a chronic bacterial infection of the skin), uses of the various product classes, as well as discussions relating to definitions of such classes. In addition, because the Commissioner has already taken final regulatory action against hexachlorophene (21 CFR 250.250) and the halogenated salicylamides, particularly tribromsalan and fluorosalan (21 CFR 310.508), they will not be discussed in this document.

Therefore, based upon the record before him (all data submitted, the minutes of the Panel meetings, the Panel report, and all comments), the Commissioner determines that the use of topical antimicrobial products under the following conditions is unsupported by scientific data, and in many instances by sound theoretical reasoning. The Commissioner concludes that the ingredients, labeling, and combination drugs involved should not be permitted in interstate commerce effective as of 6 months after publication of the final monograph in the FEDERAL REGISTER, until scientific testing supports their use.

CATEGORY II ACTIVE INGREDIENTS

Antimicrobial soap

Benzalkonium chloride.[1]
Benzethonium chloride.[1]
Hexylresorcinol.[1]
Iodine complexed with phosphate esther of alkylaryloxy polyethylene glycol.[1]
Iodine tincture.[1]
Methylbenezthonium chloride.[1]
Nonyl phenoxypoly (ethyleneoxy) ethanol iodine.[1]
Poloxamer-iodine complex.[1]
Triple dye.[1]
Undecoylium chloride-iodine complex.[1]
Phenol greater than 1.5 percent aqueous/alcoholic.

Health-care personnel handwash

Cloflucarban.[2]
Phenol greater than 1.5 percent aqueous/alcoholic.
Iodine complexed with phosphate ester of alkylaryloxy polyethylene glycol.
Iodine tincture.
Nonyl phenoxypoly (ethyleneoxy) ethanol iodine.
Poloxamer-iodine complex.
Triclosan.
Triple dye.[1]

Patient preoperative skin preparation

Cloflucarban.
Phenol greater than 1.5 percent aqueous/alcoholic.
Triclocarban.
Triclosan.
Triple dye.[1]

Skin antiseptic

Cloflucarban.
Phenol greater than 1.5 percent aqueous/alcoholic.
Triclocarban.
Triple dye.[2]

Skin wound cleanser

Cloflucarban.[2]
Phenol greater than 1.5 percent aqueous/alcoholic.
Triclocarban.[2]
Triple dye.[1]

Skin wound protectant

Cloflucarban.
Phenol greater than 1.5 percent aqueous/alcoholic.
Triclocarban.
Triple dye.[1]

Surgical hand scrub

Cloflucarban.
Iodine tincture.
Phenol greater than 1.5 percent aqueous/alcoholic.
Triclocarban.
Triclosan.
Triple dye.[1]

A. PHENOL GREATER THAN 1.5 PERCENT AQUEOUS/ALCOHOLIC SOLUTION

The Commissioner has reviewed the Panel's report on a number of products containing phenol in a variety of vehicles.

The Commissioner concludes that phenol in concentrations greater than 1.5 percent in aqueous or alcoholic vehicles is not safe for general use as an OTC antimicrobial agent in man.

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[1] Placed in Category II due to a phyiscal and/or chemical incompatability in formulation.

[2] Category II when formulated in any manner other than as a bar soap.

[3] Category II for use outside the neonatal nursery.

Several references document the toxicity of phenol when applied topically. For example, authors have noted that a 2 percent ointment resulted in blood levels of 0.8 milligram (mg) of free phenol or 2.3 mg of conjugated phenol per 100 milliliters (ml) of blood. It should be noted that 30 mg of free and 1 mg of conjugate are fatal concentrations. One to 5 percent phenol applied as a dressing or compress has caused gangrene.

It has also been recorded that 2 percent and higher concentrations of phenol an aqueous vehicles have caused serious hazards, including gangrene, anesthesia, mummification, and even coma. Phenol is more soluble in alcohol than in water and would penetrate to deeper layers of the skin, producing severe burns, and might be systemically absorbed in higher concentrations.

The acute systemic toxic effects of phenol in man and animals is observed primarily as an effect on the central nervous system. Sudden physical collapse has been observed in man after systemic exposure associated with other effects such as myocardial depression and marked blood pressure fall. There may also be marked dyspnea and a decrease in body temperature. These systemic effects are related to the amount of free phenol in the blood. A blood level of 30 mg of free phenol per 100 ml of blood can be fatal, and death is usually the result of respiratory failure.

Chronic poisoning in man results in digestive disturbances, such as vomiting, difficulty in swallowing, diarrhea, and anorexia. Nervous disorders, such as headache, fainting, vertigo, and mental disturbances also occur. There is a report that phenol is a carcinogen in animal tissue. In severe cases, sometimes fatal, there may be extensive damage to the kidneys and liver. Most of the reported cases of chronic poisoning have resulted from ingestion or inhalation. However, it is possible that repeated topical application over large surfaces of the body could lead to the systemic effects described above.

After absorption, phenol is excreted in the free form in the urine or is conjugated in the liver to the glucuronide or sulfate, prior to excretion in the urine. Some is expired in the air. In the rabbit, after a single oral dose, 23 percent was oxidized in the body to carbon dioxide and water plus pyrocatechol and hydroquinone. Of the 72 percent excreted in the urine, 48 percent was excreted as the free phenol and 52 percent as the conjugates. Only 1 percent of the total administered dose was excreted in the feces. In addition, two authors have reported that phenol is a cocarcinogen in animals.

With local dermal application of high concentrations, a pellicle of denatured protein is formed, which may turn red and slough, leaving a brown stain. Prolonged contact of phenol with the skin, resulting in deep penetration of the skin, can produce gangrene and necrosis. Ochronosis (darkening of the tissue) can also result from prolonged dermal contact. If applied to mucous membranes or swallowed, phenol can cause swelling, corrosion, necrosis, and hemorrhages of the mucous membranes of the throat or gastrointestinal tract.

In the past, preparations of 1 to 5 percent phenol in aqueous solutions have been used with dressing and compresses. This has resulted in gangrine, primarily when applied to fingers and toes. Preparations containing 1 to 2 percent phenol have been formulated frequently in salves or ointments and with vegetable oil or calamine lotion for antipruritic effects. The use of 2 percent phenol ointment has resulted, as reported above, in blood levels of 0.8 mg of free phenol and 2.3 mg of conjugated phenol per 100 ml blood. Blood levels of phenol attained after application of phenol in liquid preparation have not been presented.

The use of low concentrations of phenol (1 to 2 percent) in ointments, lotions, salves, or solutions can cause toxicity leading to severe incidence of gangrene with prolonged contact and/or occlusion of the treated area. Rat studies have shown that a 1.78 percent phenol-liquid petrolatum solution will cause gangrene in the same period of time. The posure in 2 to 3 days. A 4.15-percent aqueous phenol solution caused gangrene in the same period of time. The use of oil in the formulation may enhance the toxicity.

Camphor also has been used in formulations containing phenol. Camphor may in fact retard the absorption and availability of phenol from the solution. However, the local toxicity of phenol in a camphor-containing preparation depends upon the aqueous/phenol phase resulting from the presence of tissue fluids or perspiration. Camphor, if present with phenol, will "hold" the phenol, as is evidenced by the study that demonstrated that, while 60 percent of the phenol in a saturated solution of liquid petrolatum is in the aqueous phase, only 22 percent of the phenol in a 4.6 percent phenol/10 percent camphor combination in liquid petrolatum is in the aqueous phase. When the camphor concentration was raised to 21 percent, only 10 percent of the phenol was in an aqueous phase. The presence of camphor also retards the absorption of phenol after topical application.

A 1-hour exposure of the rat tail to a 4.8 percent aqueous phenol solution resulted in the absorption of 71 mg of phenol; whereas, the presence of 10.9 percent camphor combined with 4.5 percent phenol resulted in the absorption of only 16 mg phenol.

B. CLOFLUCARBAN

After reviewing the data and the Panel's recommendation, the Commissioner concludes that cloflucarban is not generally recognized as safe or effective for use as a patient preoperative skin preparation, skin antiseptic, skin wound protectant, and surgical hand scrub. This ingredient has been marketed only as a bar soap to be used with water; no safety and effectiveness data for its use in products in the other classes were submitted to the OTC drug review; no data were received or reviewed by the Panel; and no comments were received by the Commissioner in response to the proposed monograph. The ingredient is therefore outside this monograph and may not be marketed in products in any product classification except skin wound cleanser, health-care personnel handwash (only when used in a bar soap), and antimicrobial soap (for which it is classified in Category III) unless there exists an approved new drug application.

C. TRICLOCARBAN

After reviewing the data and the Panel's recommendation, the Commissioner concludes that triclocarban is not generally recognized as safe or effective for the following product uses: Patient preoperative skin preparation, skin antiseptic, skin wound protectant, surgical hand scrub, health-care personnel handwash, and skin wound cleanser (except when formulated in a bar soap). This ingredient has never been marketed or formulated in any of these product classes; no safety and effectiveness data for these product classes were submitted to the OTC drug review; no data were received or reviewed by the Panel; and no comments were received by the Commissioner in response to the proposed monograph. The ingredient is therefore outside this monograph and may not be marketed in products in any product classification except antimicrobial soap, unless there exists an approved new drug application or an amendment to the applicable OTC drug monograph.

D. TRICLOSAN

The Commissioner recognizes that a health-care personnel handwash, patient preoperative skin preparation, or a surgical hand scrub are designed primarily for extensive use in the hospital or other closed environment.

The Commissioner concludes that formulations containing this ingredient should not be used in these environments because of possible increased one-way environmental pressures toward gram-negative (especially *Pseudomonas*) infections. (See part III. Paragraph C. below—Triclosan.) He therefore concludes that triclosan in the above-mentioned topical antimicrobial product classes is not generally recognized as safe and effective and is misbranded.

CATEGORY II LABELING

The Commissioner has reviewed the claims which the Panel found misleading to the consumer and which they recommended be placed in Category II. While no discussion of these claims was included in the report, the Commissioner has reviewed the administrative record and concludes that, with the exception of the claim, "controls infection," as noted in paragraph 34, these claims are vague, false, or misleading and that their use with topical antimicrobial products described in this document will result in the product being misbranded. His spe-

cific conclusions and reasons therefore are set forth as follows:

A. "SPEEDS, PROMOTES OR AIDS HEALING" OR "HEALS (WOUNDS)"

The above claims imply to the consumer that antimicrobial products play a primary role in the healing process and thereby shorten healing time. In fact, their only action is to remove pathogenic microorganisms that might slow the healing process from the wound. This allows the body's healing process to follow its usual course at a normal rate. Since the ingredients reviewed do not directly affect healing, as the claims imply, the Commissioner concludes that these or similar phrases are false and misleading to the average consumer.

B. "DISINFECTS" OR "SANITIZES" THE SKIN OR WOUND

The Commissioner realizes that these terms are intended to imply cleansing of human tissue. However, there is some discrepancy between the commonly understood or lay meaning of these terms and their scientific meaning. The Commissioner is concerned that, as he attempts to set general standards in this area, terms and claims not be ambiguous or have dual meanings. Such is the case with the terms "disinfect" and "sanitize," which when used scientifically, refer to antimicrobial action or inanimate objects, but when used in the labeling of antimicrobial products, refer to antimicrobial activity on the body (39 FR 33114).

The Commissioner concludes that to assure clarity and conciseness of the meaning of these claims, as well as to eliminate the confusion caused by the dual meaning, their use should be limited to denoting antimicrobial action only on inanimate objects. Therefore, the above claims (or similar claims) will be considered misleading when applied to the use of topical antimicrobial products on humans.

C. "STERILIZES" THE SKIN OR WOUND

"Sterilize" is defined and commonly understood to mean a process by which all microorganisms are removed from an object. Such removal would include removal from the skin of both pathogenic and nonpathogenic microrganisms. The concentrations of ingredients in the OTC topical antimicrobial products under review are not high enough to render the skin or wound completely free from all microorganisms. Further, as noted by the Panel in its report, complete elimination of all microorganisms is not necessarily desirable since it would include removal of the normal microbial flora of the skin. The claim "sterilizes" the skin or wound, therefore, is presumably intended to apply only to the destruction of pathogenic microorganisms. However, the ambiguity between the intended meaning and the actual definition of the term "sterilize" renders the claim vague and misleading.

D. "ENSURES BACTERIALLY CLEAN SKIN"

While the purpose of this claim may be to suggest removal only of pathogenic organisms from the skin, the Commissioner concludes that it is reasonably likely to convey to many consumers the idea that removal of all microorganisms from the skin will result from the use of products for which such claims are made, and that such a result is beneficial. As explained above, the removal of all bacteria on the skin cannot be accomplished with the concentrations of the ingredients found in OTC topical antimicrobial products. Further, the removal of all microorganisms including normal flora is not necessarily desirable. The Commissioner concludes that this or similar phrases are vague and misleading when applied to use of topical antimicrobial products on humans.

III. THE COMMISSIONER'S CONCLUSIONS ON THE CATEGORY III RECOMMENDATIONS

The Commissioner's conclusions on and restatement of the Panel's recommendations and conclusions for Category III are set forth below. The Commissioner adopts these findings by restating the appriate sections of the Panel's findings in this document, with modifications for clarity and regulatory accuracy, as well as for new data and information that have come to his attention. Changes based on new data and information are discussed in the preamble. Gratuitous or unsupported statements have been excluded. The Commissioner's agreement with comments suggesting modification of the Panel's findings are incorporated in the Commissioner's restatement of them.

As with the discussion of Category II above, the Commissioner is not restating those parts of the Panel's findings that are not directly relevant to his decision on the content of Category III.

Therefore, based upon the record before him (all data submitted, the minutes of the Panel meetings, the Panel report, and all comments), the Commissioner determines that adequate and reliable scientific evidence is not available at this time to permit final classification of the following conditions pertaining to the use of topical antimicrobial products.

The Commissioner concludes that category III ingredients may be permitted to remain in use until 2 years after publication of the final monograph in the FEDERAL REGISTER provided tests and studies of any such product are conducted according to the testing guidelines below to satisfy the questions raised in this document. (See part IV. below—FINAL TESTING GUIDELINES FOR SAFETY AND EFFECTIVENESS OF OTC TOPICAL ANTIMICROBIALS.) For further requirements relating to Category III testing, see 42 FR 19137 (April 12, 1977).

CATEGORY III ACTIVE INGREDIENTS

Antimicrobial soaps

Cloflucarban.
Para-chloro-meta-xylenol.
Povidone-iodine complex.
1.5 percent phenol or less aqueous/alcoholic.
Triclocarban.[1]
Triclosan.[1]

Health-care personnel handwash

Benzalkonium chloride.
Benzethonium chloride.
Cloflucarban.[1]
Hexylresorcinol.
Iodine complexed with phophate ester of alkylaryloxy polyethlene glycol.
Methyl-benzethonium chloride.
Nonyl phenoxypoly (ethyleneoxy) ethanol-iodine.
Para-chloro-meta-xylenol.
Povidone-iodine complex.
1.5 percent phenol or less aqueous/alcoholic.
Poloxamer-iodine complex.
Triclorcarban.[1]
Undecoylium chloride-iodine complex.

Patient preoperative skin preparation

Benzalkonium chloride.
Benzethonium chloride.
Hexylresorcinol.
Iodine complexed wtih phosphate ester of alkylaryloxy polyethylene glycol.
Methylbenzethonium chloride.
Nonyl phenoxypoly (ethyleneoxy) ethanol-iodine.
Para-chloro-meta-xylenol.
1.5 percent phenol or less aqueous/alcoholic.
Poloxamer-iodine complex.
Povidone-iodine complex.
Undecoylium chloride-iodine complex.

Skin antiseptic

Benzalkonium chloride.
Benzethonium chloride.
Hexylresorcinol.
Iodine complexed with phosphate ester of alkylaryloxy polyethylene glycol.
Iodine tincture.
Methyl-benzethonium chloride.
Nonyl phenoxypoly (ethyleneoxy) ethanol-iodine.
Para-chloro-meta-xylenol.
1.5 percent Phenol or less aqueous/alcoholic.
Poloxamer-iodine complex.
Povidone-iodine complex.
Triclosan.
Triple Dye.[2]
Undecoylium chloride-iodine complex.

Skin wound cleanser

Cloflucarban.[1]
Iodine complexed with phosphate ester of alkylaryloxy polyethylene glycol.
Iodine tincture.
Nonyl phenoxypoly (ethyleneoxy) ethanol-iodine.
Para-chloro-meta-xylenol.
1.5 percent phenol or less aqueous/alcoholic.
Poloxamer-iodine complex.
Povidone-iodine complex.
Triclocarban.[1]
Triclosan.
Undecoylium chloride-iodine complex.

Skin wound protectant

Benzalkonium chloride.
Benzethonium chloride.
Hexylresorcinol.
Iodine complexed with phosphate ester of alkylaryloxy polyethylene glycol.
Iodine tincture.
Methylbenzethonium chloride.
Nonyl phenoxypoly (ethyleneoxy) ethanol-iodine.
Para-chloro-meta-xylenol.

[1] Category III only when formulated in a bar soap to be used with water.
[2] Restricted to use only in neonatal nursery.

1.5 percent Phenol or less aqueous/alcoholic.
Poloxamer-iodine complex.
Povidone-iodine complex.
Triclosan.
Undecoylium chloride-iodine complex.

Surgical hand scrub

Benzalkonium chloride.
Benzethonium chloride.
Hexylresorcinol.
Iodine complexed with phosphate ester of alkylaryloxy polyethylene glycol.
Methylbenzethonium chloride.
Nonyl phenoxypoly (ethyleneoxy) ethanol-iodine.
Para-chloro-meta-xylenol.
1.5 percent phenol or less aqueous/alcoholic.
Poloxamer-iodine complex.
Povidone-iodine complex.
Undecoylium-chloride iodine complex.

In addition, the Commissioner wishes to note that after extensive review of the administrative record and the data submitted in comments, he has determined that there are sufficient data to consider poloxamer 188 as generally recognized as safe and effective and not misbranded (Category I) for use as a skin wound cleanser.

CATEGORY III LABELING

Since the Panel suggested no Category III claims and none were suggested in the comments to the report, the Commissioner concludes there are none. He is therefore deleting any discussion of Category III claims in this document.

GENERAL COMMENT APPLICABLE TO ALL INGREDIENTS IN CATEGORY III

The Commissioner concludes that adequate and well-controlled studies are not available at this time to permit the final classification of the active ingredients listed above.

The hexachlorophene experience has made apparent to the scientific community that toxic levels of antimicrobial chemicals applied to the skin are absorbed into the body. The greatest lack of substantial data is in the following areas: retention and/or substantivity, absorption, blood level, organ distribution, possible tissue depositing, and excretion.

A. CLOFLUCARBAN

The Commissioner has reviewed the safety and effectiveness data submitted and concludes that cloflucarban (TFC, CF_3, 3-trifluoromethyl, 4,4' dichlorocarbanilide) is effective as an antimicrobial soap but that adequate safety data are not yet available to permit its final classification in this product class.

The Commissioner concludes that enough data were submitted to convince him that there is no known hazard to the public from the continued use of cloflucarban in antimicrobial soaps at the maximum concentration and for the interim period specified below. The basis for this was the oral LD_{50} of cloflucarban in rats as compared with hexachlorophene. The oral LD_{50} for cloflucarban is reported to be in excess of 5 gm/kg body weight while the LD_{50} for hexachlorophene is only 0.12 gm/kg. Also, based on blood level data for cloflucarban, which are not complete at this time, the Commissioner does not consider cloflucarban to be as toxic as hexachlorophene. Therefore, the Commissioner concludes that cloflucarban (or a combination of cloflucarban with triclocarban), when used in antimicrobial soaps, should not exceed a total concentration of 1.5 percent and that this should be permitted to extend for a period of 2 years following publication of the final monograph in the FEDERAL REGISTER in order to allow interested parties time to conduct the necessary research to correct the deficiencies listed below.

The Commissioner still finds several areas of deficiencies in the safety data base. One of these is the lack of blood level data following topical application. In fact, he has received no data showing the following:

1. Substantivity of cloflucarban to the skin following one and several baths using a cloflucarban-containing antimicrobial soap.

2. Degree of absorption of cloflucarban following deposition on the various types of skin (young, mature, aged, diseased).

3. Peak blood levels following multiple baths.

4. Metabolic rate of cloflucarban excretion from the body.

5. Tissue storage of cloflucarban.

It is the Commissioner's opinion that final classification of cloflucarban for use in antimicrobial soaps cannot be made until such data are provided.

From a purely toxicological viewpoint, the Commissioner believes that inadequate data were submitted showing a dose/effect relationship. Conflicting data were submitted that were at such variance that interlaboratory differences could not possibly account for the discrepancies. For example, data showed that cloflucarban caused testicular effects in rats after 4, 8, 11, and 13 weeks of study at the lowest oral feeding level, 25 mg/kg, and liver changes at 1,000 mg/kg. This study showed that a "no-effect" oral feeding level was somewhere below 25 mg/kg. In contrast to this study, another study indicated that the "no-effect" oral level was 100 mg/kg with no testicular or other pathologic finding.

The Commissioner therefore was presented two controlled studies with widely varying results. It is the conclusion of the Commissioner that these discrepancies be resolved through adequately controlled research, which will show the "effect" and "no-effect" level in the same study. Just as important is a determination of the "effect" and "no-effect" blood level of cloflucarban. As a word of caution, it should be pointed out that the Commissioner was presented suggestions that an adequate analytical procedure for cloflucarban in biologic fluids was not available.

In view of these conflicting data and in the absence of definitive data on absorption through human skin, the Commissioner concludes that a limit of 1.5 percent cloflucarban (or a combination of cloflucarban and triclocarban) be set until such time as adequate data relating blood levels and toxic effects are made available.

Data submissions to the Commissioner are adequate at this time to assure him that cloflucarban has no significant potential for the induction of carcinogenesis, teratogenesis, or mutagenesis. The Commissioner therefore does not consider these to be problem areas.

The Commissioner is concerned about the potential for cloflucarban to cause contact sensitization. More to the point, perhaps, is the lack of adequate research addressing this potential. There are reports drawing attention to contact sensitization concerning cloflucarban. These authors indicated that the potential for contact sensitization from cloflucarban is greater than that from triclocarban, but far less than that from certain other antimicrobial agents. On the other hand, the existence of photosensitization cases was not found and therefore does not have to be studied.

In summary, the Commissioner concludes that cloflucarban or a combination of cloflucarban with triclocarban can be used in antimicrobial soap at a total concentration not to exceed 1.5 percent and only for a period of 2 years following publication of the final monograph in the FEDERAL REGISTER. The toxicity studies outlined in the guidelines will be required and should include determination of the oral toxicity, including target organ determination, with blood levels and "effect" and "no-effect" dose in the same study.

B. THE COMBINATION OF TRICLOCARBAN AND CLOFLUCARBAN IN BAR SOAP

The Commissioner is placing the combination of triclocarban and cloflucarban in Category III. These two chemicals are quite similar in their use, mode, and spectrum of antimicrobial action, and, in all likelihood, toxicity. However, it is the view of the Commissioner that additional data are needed on the cloflucarban component. Also, no data were submitted on the toxicity of the combination of ingredients, although it is the understanding of the Commissioner that such studies are currently being conducted. If used in combination with triclocarban, toxicity studies will be required to demonstrate that there is no increased toxicity with the combination. The studies to characterize the toxicity of the individual chemicals, as outlined in the safety testing guidelines under the discussion of triclocarban and cloflucarban, also apply to the combination and should include determination of substantivity, absorption, distribution, blood levels, excretion, and effect/no-effect dose with the establishment of toxic effects, especially on the target organ determined in the same study.

Until adequate studies are submitted to make a final determination, the Commissioner concludes that there should be a limitation of the total combination of triclocarban and cloflucarban to 1.5 percent for a period not to exceed 2 years after publication of the final monograph in the FEDERAL REGISTER.

C. TRICLOSAN

The Commissioner has reviewed additional data submitting during the com-

ment period in response to questions raised by the Panel. The Panel stated that further studies are necessary to detremine whether the triclosan molecule, the metabolite(s) or both produce liver toxicity in rats and dogs. In addition, the Panel concluded that more data on human blood levels following topical application were needed. A variety of skin areas, types, and conditions should be studied. The Panel expressed concern over the possibility of increased blood levels of triclosan resulting from widespread use of triclosan in soaps and deodorant products and recommended that this should also be investigated.

After reviewing these additional data, the Commissioner concludes that triclosan should remain in Category III for use in antimicrobial bar soap because adequate data are not yet available to permit final classification of this ingredient. Even though industry has submitted additional data (discussed below) subsequent to the Panel's report, questions have arisen regarding the validity of these studies as well as some data originally reviewed by the Panel.

Triclosan is one of the most highly absorbed antimicrobial ingredients reviewed by the Antimicrobial Panel. Even though additional data were submitted during the comment period, human absorption data from exaggerated human use (similar to the data from use of radiolabeled triclocarban discussed above) are not available for triclosan. The results of such a study are critical to assessing whether the increasing number of products now being formulated with triclosan, such as cosmetics, infant clothing, and diaper rinses will increase the blood levels of triclosan to an appreciable degree. Because data contained in a recently received comment have shown that triclosan has a higher rate of absorption than other currently marketed antimicrobials used in bar soaps (i.e., approximately 3 percent topical absorption for triclocarban compared to approximately 12 percent topical absorption for triclosan), concentrations of triclosan in antimicrobial bar soaps must be limited to 1 percent.

The Commissioner finds that the safety factor in submitted data is based on the assumption that the population will be exposed to triclosan only in antimicrobial soaps and related antimicrobial products. This is no longer the situation, and in view of the increasing use of triclosan in consumer products, the final resolution of risk to benefit, particularly with respect to increasing body burden of triclosan, cannot be made at this time.

In addition, adequate safety and effectiveness data are not yet available to permit final classification for this ingredient in skin antiseptics, skin wound cleansers, and skin wound protectants. From the data submitted, the Commissioner concludes that there is no known hazard to the general public from the use of triclosan in concentrations not greater than 1 percent. He therefore concludes that triclosan should be permitted for use in antimicrobial bar soap, as a skin antiseptic, skin wound cleanser and skin wound protectant and allowed to be sold to the general public for a period of 2 years following publication of the final monograph in the FEDERAL REGISTER in order to allow interested parties time to conduct the necessary research to supply data in the areas indicated as deficient in the following summary:

It has been shown in animal experiments that triclosan can be absorbed through intact skin. This has been verified and reported in a submission which details human blood levels following the use of a triclosan-containing soap on intact skin.

The primary target organ for toxicity from triclosan is the liver. There is still a question as to whether the damage to the liver is due to the intact molecule, a metabolite, or a combination of the two (triclosan and/or triclosan metabolite).

A subchronic (90-day) oral study in dogs revealed liver damage at blood levels of 67.4 parts per million (ppm) total triclosan (free triclosan plus metabolite) resulting from an oral dose of 25 mg/kg/day. A no-effect oral dose of 12.5 mg/kg/day, in the same study, resulted in a total blood level of 36.1 ppm. Similar studies, using the same oral dosage regimen, showed liver toxicity in dogs, but actual blood levels were not measured. The dose-related histopathological damage in the dogs was described as periportal to midzonal hepatoxytic degeneration, which led to focal necrotic hepatitis. This change appears to be reversible when exposure to triclosan is terminated. In other studies, when triclosan was administered in the diet to dogs or rats for 90 days at doses equivalent to those used in previously discussed studies, no liver damage resulted. Triclosan absorption varies in animal species; therefore, the amount of intestinal and topical absorption needs to be established.

Taking into consideration animal toxicity and human absorption and blood levels, safety factors were calculated. It was found in subchronic 90-day dog studies that the highest no-effects dose was 12.5 mg/kg. The absolute dose given the dog was 75 mg (12.5 mg/kg X 6 kg/dog). Extrapolating to man, by surface area, using the technique of Paget and Barnes, (Panel report (39 FR 33113)), the no-effect level might be expected to be 232.5 mg in the human. The value was calculated by multiplying the absolute dose in dogs showing no-effect by the conversion factor for surface area (75 mg X 3.1). Similar calculations were also possible with a 90-day monkey study.

If, as assumed by the Panel, an antimicrobial bar soap contains 1 percent triclosan as the active ingredient and an average bath consumes 7.0 gm of soap, then the total available triclosan per bath would be 70 mg. Since 1 percent of the 70 mg of the available triclosan remains on the skin then a total of 0.7 mg of triclosan is available for absorption after each bath. Also, since the data show that approximately 8.9 percent of the 0.7 mg of triclosan is absorbed, then 0.062 mg would be in the blood. Thus, the following hypothetical safety factor, using surface area, can be calculated:

$$\frac{\text{232.5 mg (expected no-effect dose level in man)}}{\text{0.062 mg (expected exposure dose in man from one bath)}} = \text{3,754-fold safety factor}$$

Another way to calculate a safety factor is to assume that an average size human has 5,000 ml of blood. Since the data show that 0.062 mg of triclosan is instantaneously absorbed from the skin after exposure, the concentration of free triclosan in the blood would be approximately 12 parts per billion (ppb). Assuming that some persons take two baths per day, and that the total triclosan per bath is absorbed and accumulates, the blood level would be 24 ppb. Data from the submission suggest that rapid conversion of free triclosan to the glucuronide occurs and that within a few minutes, most of the absorbed triclosan exists only as the metabolite.

If the lowest "no-effect" blood level data (36,110 ppb triclosan/triclosan metabolite) is taken in dogs, and recognizing that the data were reported from a 90-day study, the following safety factor could be calculated:

$$\frac{\text{36,100 ppb}}{\text{12 ppb (blood level of triclosan from a single bath)}} \text{ 3,000-fold safety factor.}$$

$$\frac{\text{36,100 ppb}}{\text{24 ppb (blood level of triclosan from two baths)}} = \text{1,500-fold safety factor.}$$

Based on the highest "effect" blood level (67,400 ppb triclosan/triclosan metabolite), the following calculation could be made:

$$\frac{\text{67,400 ppb}}{\text{12 ppb (single bath)}} = \text{5,600-fold safety factor.}$$

or

$$\frac{\text{67,400 ppb}}{\text{24 ppb (two baths)}} = \text{2,800-fold safety factor.}$$

Data from humans revealing a blood level of 44 ppb of triclosan/triclosan metabolite allowed the Panel to make the following calculations:

$$\frac{\text{67,400 ppb (blood level at effect dose in dogs)}}{\text{44 ppb}} = \text{1,531-fold safety factor.}$$

$$\frac{\text{36,100 ppb (blood level at no effect dose in dogs)}}{\text{44 ppb}} = \text{821-fold safety factor.}$$

These calculations would indicate a substantial safety factor, but it should be pointed out that studies relating blood levels to toxic effects, are short-term studies. Humans may be exposed to bar soap daily over their entire life span. The Panel made several assumptions based on unresolved data, particularly on the degree of substantivity and rate and amount of absorption. But these are only assumptions and must be tested. Research should be on humans in various age groups and with varying skin conditions.

No evidence of potential mutagenesis or teratogenesis was found in studies on various rodent species. The study on the carcinogenicity potential of triclosan has been declared invalid by the agency and must be repeated or validated.

Data indicate that triclosan cannot be considered a primary sensitizing or photosensitizing agent in animals or in humans. But studies have not eliminated possible cross-reactivity following previous sensitization with hexachlorophene, salicylanilides, or carbanilides and further cross-sensitization studies should be performed. (The halogenated salicylanilides have been removed from OTC use (40 FR 50530, October 30, 1975; see 21 CFR 310.508).

The Commissioner now feels that adequate data concerning elimination and toxicity in young animals have been submitted. Research in young animals with unavailable glucuronide systems has been conducted in order to define the toxicity potential for human infants and individuals with inadequate liver function. Recently received data, including a 90-day monkey study, establish the rate of absorption of triclosan and indicate that rhesus monkey neonates can eliminate topically applied triclosan. Although the major route of elimination of triclosan from the body (conjugation to the glucuronide in the liver) is not available to newborn primates, an alternate means of elimination (sulfonation) is well developed at birth and apparently permits subhuman neonates to safety handle any absorbed triclosan.

However, as noted in paragraph 18 above, the Commissioner sees little or no need to use antimicrobial soaps on newborn babies. Also, there are inadequate data to prove that human infants, who do not have an adequate glucuronide pathway, can adapt to excrete triclosan by sulfonation, as can rhesus monkeys. Thus, in order not to risk exposure of human neonates to inordinately high blood levels of triclosan, triclosan will have a label warning "Do not use this product on infants under 6 months of age".

Data submissions and a series of reports regard to the antimicrobial activity of triclosan have been reviewed. These reports suggest that numerous gram-positive bacteria are susceptible to its action at levels comparable to other substituted phenols, such as hexachlorophene. However, some gram-positive skin bacteria appeared somewhat less susceptible than others, and the lack of susceptibility of the gram-positive streptococci is a potential hazard. In attempts to define the spectrum of triclosan, some of the gram-negative bacterial strains listed in the reports were revealed to be susceptible to triclosan. Those gram-negative bacteria showing in vitro susceptibility to triclosan included strains of the various coliforms, *Proteus* and *Salmonella*. One type of gram-negative organism of increasing importance in the hospital environment that was found to be quite resistant was *Pseudomonas aeruginosa*. Other microorganisms showing low levels of susceptibility included various fungi and viruses, such as the polio virus. Influenza, adeno- and vaccinia viruses are inhibited at a lower concentration. The reports suggest that reduction of the number of microorganisms in the skin microflora with the use of triclosan in soaps is similar to that with other bisphenols.

Some reports suggest that *Pseudomonas* can be selectively established at high levels on the skin with the topical use of bisphenols. In addition, triclosan can be utilized for the selective isolation of *Pseudomonas* from materials containing both gram-positive and gram-negative organisms. These materials include food and microflora samples from the skin. This isolation is facilitated with the use of a patented *Pseudomonas* isolation triclosan-containing agar.

Triclosan differs from some other bacteriostatic chemicals active primarily against gram-positive bacteria, in that it does have limited in vitro and probable in vivo activity against some gram-negative bacteria, but unfortunately not against *Pseudomonas*. With the widespread use of antibiotics and disinfectants selectively active, primarily against gram-positive bacteria in the hospital environment, gram-negative, nosocomial infections, especially *Pseudomonas*, are increasingly life-threatening. With the environmental pressures being pushed in one direction (one-way selective pressure) toward the selection of gram-negative organisms, i.e., *Pseudomonas*, in the hospital environment, unexpected reservoirs and mechanisms of transmission are being reported. It is essential to eliminate sources of gram-negative bacteria in particular areas of the hospital such as burn units, neonatal nurseries and intensive care units in which immunosuppressive drugs are administered. One study describes the use of a triclosan-containing soap in hospitalized and immunosuppressed patients. This study reports the results of the bathing of leukemic patients in a protected environment (Life Island) with a bar soap containing 1 percent tribromsalan and 1 percent triclosan. The authors report reduction in total counts of staphylococcal species, including some potential pathogens and gram-negative bacteria on various body sites. It is the Commissioner's view that the results of this in vivo study cannot be projected to a normal environment.

The patients in this uncontrolled study were all immunosuppressed and receiving concomitant antibiotic therapy, both oral and topical. In addition, the skin sampling and culture techniques were not optimal for the isolation of *Pseudomonas* from the skin. The serious possibility of carryover of inhibitory antimicrobial residue from topical therapy would invalidate the cultural results. And there is a risk involved in using a soap that has no activity against *Pseudomonas* on immunosuppressed patients. A subsequent study of a similar type concluded that, although 76 percent of aerobic bacteria, including gram-negative bacteria, were eliminated by cleansing with a soap containing a combination of triclosan and tribromsalan, strains of potential pathogens such as *Enterobacter* species, a *Klebsiella* species, *Proteus* species, and *Pseudomonas aeruginosa* persisted. Thirty-three percent of the patients had persistent pathogenic bacteria and 40 percent had persistent fungi. Despite intensive systemic and topical antibiotic therapy and washing with an antimicrobial soap as a protective measure, the organisms persisting are those most likely to cause fatal infections in these seriously ill patients.

The Commissioner concludes that clinical effectiveness in the prophylaxis and treatment of superficial pyrogenic infections of the skin has not been established.

The Commissioner notes that triclosan can be used in an isolation medium which will permit the selective isolation of *Pseudomonas* from the skin. Additionally, it is known that triclosan is effective in vitro primarily against gram-positive organisms and against some gram-negative organisms, but is not effective against *Pseudomonas*. Human skin is a culture medium superior in many instances to those devised by microbiologists. This raises the possibility that use of triclosan by health-care personnel in closed environments such as hospitals and nursing homes would act to selectively promote the growth of *Pseudomonas*, especially on their hands, in an environment where *Pseudomonas* is ubiquitous and may be life-threatening to many patients.

Because of this potential for influencing the gram-negative population and/or the addition of another potential selective agent for *Pseudomonas*, the Commissioner concludes that triclosan-containing products should not be used in the hospital or other closed environments, such as nursing homes, where individuals are present who may be highly susceptible to infection with microorganisms not normally pathogenic (opportunistic pathogens). Accordingly, the Commissioner has determined that triclosan as a single ingredient is not safe for use in health-care personnel handwashes, surgical scrubs, and patient preoperative preparations.

This restriction on the use of triclosan also applies to any combination products containing triclosan unless the deficiency in the microbial spectrum is compensated for by another antimicrobial ingredient. Triclosan should be used only in products where there is no exposure to persons who have debilitating diseases, or who are physically debilitated, or immunologically compromised, or where the closed environment in the hospital or other institution would possibly allow the shift of environmental pressures toward *Pseudomonas*.

Many animal toxicity studies for this ingredient have been submitted, and they are discussed above. Before triclosan can be considered safe as a skin wound cleanser, skin wound protectant or skin antiseptic, further work is necessary to determine what produces the toxic effect. More data on human blood levels following topical application on abraded skin are needed, and a variety of skin areas, types, and conditions should be studied.

The Commissioner concludes that in vitro data indicate that triclosan has

some activity against some gram-negative microorganisms, but that further verification of the spectrum is required, as well as in vivo demonstration of activity against *Proteus, Salmonella,* and *Pseudomonas aeruginosa* before this ingredient can be placed in Category I as a skin antiseptic or skin wound protectant.

The Commissioner concludes that there are insufficient data to demonstrate whether it is the triclosan molecule or its metabolite(s) that cause liver toxicity. It is also unclear whether a newborn can metabolize and eliminate triclosan, since the new born does not have an adequately developed glucoronide conjugating system. In the absence of these data the Commissioner has determined that infants should not be exposed to triclosan. Labeling must contain a warning to prohibit use of any triclosan-containing bar soap on infants under 6 months of age.

Data submitted after the publication of the Panel Report indicate that absorption of triclosan is significant after topical administration and is increased with occlusion such as clothing. Further complicating the issue is the evidence presented by these studies that some persons metabolize and eliminate triclosan or its metabolite(s) much more slowly than others. These studies indicate that hand scrubbing combined with even one shower increase the levels of triclosan and its metabolite(s), especially in persons who are slow metabolizers, perhaps as much as a thousandfold. After reviewing these data, the Commissioner concludes that there is not sufficient evidence to determine the total blood level resulting from repeated or exaggerated use of triclosan bar soaps, as with daily showers. More studies are necessary to demonstrate absorption from different body areas and increased doses to which the bar-soap user may be exposed.

The Commissioner is concerned about the multitude of sources from which the consumer can, often unknowingly, be exposed to triclosan. A variety of cosmetic products contain triclosan, and the Commissioner is aware that the Environmental Protection Agency's Office of Special Pesticide Review is presently preparing a report about the proliferation of triclosan-containing products marketed to the American consumer. If the number of sources of triclosan appears dangerously high, the Commissioner may conclude that the availability of triclosan should be curtailed, especially in bar-soaps which provide total body exposure on a repeated daily basis.

The Commissioner has carefully reviewed the animal data submitted to the Panel and that submitted subsequent to publication of the Panel's report and proposed monograph, and has determined that certain key animal studies describing the toxicity and metabolism of triclosan must be validated or repeated before these studies can be relied upon to move triclosan from Category III to Category I.

D. TRICLOCARBAN

The Commissioner had determined that the only permitted use of triclocarban (TCC, 3, 4, 4'-trichlorocarbanilide) at the present time should be as an antimicrobial ingredient in bar soap and only when used as a health-care personnel handwash, skin wound cleanser, or antimicrobial soap.

The Commissioner reviewed the available effectiveness and safety data on triclocarban and concludes that adequate data are not yet available to permit final classification of triclocarban for use in bar soap. The available evidence does not indicate that the use of triclocarban in bar soaps presents any known hazard to the general public. Based on blood level data, triclocarban does not appear to be as toxic as hexachlorophene.

A primary area of concern is the data defining the target organ for toxicity. At high blood levels of triclocarban (in excess of 200 ppm TCC/TCC metabolite), the apparent target organ in rats is the testicles. In the opinion of the Commissioner, the data relating the blood level of triclocarban to testicular damage are still not definitive. For example, one set of data in OTC Volume 020189 estimated that blood concentrations of 50 to 70 ppm TCC/TCC metabolite caused pathological changes in the testicles of test animals. More recent data from a 2-year chronic animal toxicity feeding study at 400 mg/kg/day, in OTC Volume 020165, suggest that 200 ppm TCC/TCC metabolite in the blood was an "effect level" and that a dose of 200 mg/kg/day giving a blood concentration of 100 ppm TCC/TCC metabolite was a "no-effect" level. Still other data in the OTC Volume 020139 suggested testicular lesions at oral doses lower than those which resulted in the "no-effect" blood levels mentioned above (100 ppm). In view of these conflicting data regarding blood levels and ensuing testicular damage and in view of the fact that the 2-year chronic animal toxicity feeding study mentioned in OTC Volume 020165 has recently been found to be invalid, the Commissioner regards this as an area of significant deficiency in the data. Adequate data relating blood level to target organ toxicity and "no-effect" levels will be required in the form of a 2-year chronic animal toxicity study to replace the above-described study, which the Commissioner now considers invalid.

As was shown by Maibach (Maibach, H. I., "Skin Penetration of Hexachlorophene in Living Man," Draft of unpublished paper is included in OTC Volume 020186) and confirmed by more recent data for humans, submitted as a comment to the Panel Report, triclocarban may be absorbed through human skin after topical application at a rate of approximately 14 percent of the dose applied. Elimination of triclocarban after topical application is slower than after ingestion, suggesting possible accumulation in the body. However, the adequacy of analytical methods for the detection of triclocarban and all its metabolites is still questionable, and is made more difficult by the very low levels that must be detected in blood or tissue. Based on some theoretical and some actual data, calculations of potential blood levels in man were made. It is the conclusion of the Commissioner that, until definitive data are accumulated to show blood levels in man from actual use, the concentration of triclocarban in bar soaps should be limited to 1.5 percent. The calculation that led to this conclusion follows, but it should be emphasized that the cause of testicular lesions has not yet been determined to be triclocarban (parent compound), TCC-metabolite or the combination, (TCC/TCC metabolite).

Recently received data confirm that TCC is absorbed at approximately 14 percent under human-use conditions. These data correspond closely to the calculation originally made by the Panel without this information and using certain assumptions:

If a bar soap contains 1.5 triclocarban and an average bath uses 7.0 gm of soap, the total available triclocarban, if instantaneous absorption occurred, would be 105 mg.

1.5 percent of this 105-mg triclocarban remains on the skin as a substantive agent. This retention presents to the body a total of 2.1 mg of triclocarban for absorption.

Since 14 percent of the available 2.1 mg is absorbed, as shown by Maibach, this would allow 0.294 mg of triclocarban to be absorbed from a single bath.

Since an average size human has 5,000 ml of blood, and 0.294 mg of triclocarban is absorbed, the concentration of triclocarban in the blood would be 0.075 ppm. Considering that some part of the population takes two baths per day, and assuming that the total triclocarban to which the individual was exposed accumulated during that day, the blood level would be 0.150 ppm. Data from the submissions to the Panel indicate that triclocarban as the parent compound disappears from the blood within minutes. The exact mechanism(s) of absorption and elimination is not yet clear.

If the most recent data indicating that 100 ppm total TCC (TCC/TCC metabolite) in the blood is the "no-effect" level are confirmed by the additional chronic toxicity study being required, then a safety factor could be calculated as follows:

$$\frac{100\text{ ppm}}{0.075\text{ ppm}} = 1{,}250\text{-fold safety factor (single bath)}$$

$$\frac{100\text{ ppm}}{0.15\text{ ppm}} = 625\text{-fold safety factor (2 baths per day)}$$

A major route of elimination of triclocarban from the body is reported to be via conjugation to the glucuronide in the liver. This mechanism is deficient in young animals and human infants. The Commissioner feels that although recent data have shown that an additional metabolic pathway for detoxification exists, this ingredient should be restricted

from use in infants. The label for the preparation containing the ingredient should therefore state: "Not to be used on infants under 6 months of age".

The Commissioner recognizes that the triclocarban will decompose at elevated temperatures in aqueous solution to yield chloroanilines. There are reported incidences of methemoglobinemia resulting from high-temperature decomposition of triclocarban by Johnson et al (Johnson, R., R. Navone and E. L. Larson, "An Unusal Epidemic of Methemoglobinemia," *Pediatrics*, 31:222–225, 1963). Therefore, soaps or soap products containing triclocarban should not be heated and subsequently used in or on the human body. Additionally, since chloroanilines do have a potential for inducing methemoglobinemia at higher blood levels, the chloroaniline content in bar soaps containing triclocarban should be monitored to limit it to less than 100 ppm. The Commissioner feels that adequate data were presented to the Panel to indicate that 100 ppm chloroaniline, or less, in bar soaps would present no hazard to humans even after multiple baths with such soaps.

The Commissioner further concludes from the references and data submissions reviewed that photosensitization and contact dermatitis from triclocarban are of such rarity that they present no major problem to the general user of a soap containing triclocarban.

Therefore the Commissioner concludes that the only permitted use of triclocarban should be as an antimicrobial ingredient in bar soap formulations at a concentration not to exceed 1.5 percent for use as an antimicrobial soap, health-care personnel handwash, and skin wound cleanser and only for a period of 2 years following publication of the final monograph in the FEDERAL REGISTER. During this period a 2-year chronic toxicity study in animals via oral feeding must be performed to replace the 2-year chronic feeding study involving over 400 rats, which the Commissioner has recently declared invalid. This new chronic toxicity study will be required to resolve any questions of potential testicular, brain, or splenic changes with concomitant blood levels where changes occur. Other possible depots of drug after absorption, such as the lymphatic system, should be determined in the 2-year study.

E. IODOPHORS

The Commissioner recognizes the existence of at least three categories of iodophors: (1) solubilized inorganic elemental iodine, such as iodine tincture, USP, or the aqueous iodine-iodide solubilized product; (2) iodine complexed or combined with various surfactant compounds such as poloxamer-iodine complex; and (3) iodine complexed with various nonsurfactant compounds such as PVP-iodine complex (polyvinyl pyrrolidone-iodine). The antimicrobial activity of all of these agents is dependent upon the release of elemental iodine. Iodine is recognized to be a broad spectrum antimicrobial with activity against fungi, viruses, and both gram-positive and gram-negative bacteria.

1. *Solubilized inorganic elemental iodine.* Iodine has a long history of use as a broad spectrum antimicrobial agent. There is extensive literature documenting the effectiveness of aqueous and alcoholic solutions of elemental iodine as an antimicrobial. In fact, the *United States Pharmacopeia* has listed iodine preparations since 1840. The Commissioner concludes that elemental iodine hydroalcoholic solution is safe and effective when properly used on unbroken skin as a patient preoperative skin preparation and is effective for first-aid use on minor wounds as a skin antiseptic, skin wound protectant, or skin wound cleanser. However, he has insufficient information on the effects of its irritating properties and delay in wound healing to classify it in Category I at this time.

A variety of values has been proposed for the minimum concentration at which iodine is lethal to cells. It has been reported that all microorganisms are killed by the same concentration, but the organic load (in a wound, with serum, or on the skin) and pH (acidity) may dramatically change the concentration required to achieve the desired killing effect on the skin. It is difficult to set a level of free iodine that is effective against all types of microbial flora, viruses, fungi, spores, and vegetative bacteria. However, 136 years of clinical experience with this ingredient at a 2-percent hydroalcoholic strength seems to indicate effectiveness at that strength for small minor wounds. The Commissioner, though disagreeing with the Panel's ultimate conclusion declaring iodine tincture unsafe (Category II) for "first-aid" uses, nevertheless is concerned about delay in wound healing, and therefore requiring that either of the wound-healing procedures outlined in the testing guidelines be carried out at the 2-percent hydroalcoholic strength before determining whether iodine can be considered generally recognized as safe and effective for such uses. In addition, because elemental iodine causes burns on occluded skin, label warnings for such products should contain the following warning:

"Do not apply this product with a tight bandage, as a burn may result".

2. *Iodine complexed with various surfactant compounds.* The Commissioner recognizes that elemental iodine complexed with a surfactant type "carrier" molecule reduces the amount of immediate "free" iodine, since most of the formulated iodine is bound in the complex. The Commissioner believes that effectiveness of all iodophors is dependent on the release of free iodine as the active agent and the complexing molecule acts only as a carrier. The Commissioner was not presented adequate data to determine if the complex is really a micellar solubilization of iodine at the molecular level or whether loose chemical bonding exists producing what could be termed a "sociable moiety." Indeed, the complexation of iodine with the carrier molecule is responsible for the changes in characteristics observed in staining, burning, or irritation of the skin. The amount of "free" elemental iodine in solution is a function of the equilibrium constant of each complexing formulation. If all of the "free" elemental iodine is removed from solution (as in the case of application to a wound where potentially all iodine present is bound by total organic load), then a finite period of time would be required before a new equilibrium would be established. Once the iodine is released from the complex, it acts as elemental iodine, a broad spectrum antimicrobial agent. After release of iodine, the carrier molecule remains at the site as any other similar surfactant molecule.

The Commissioner concludes from the data submissions that iodine complexed with a surfactant is an acceptable way of presenting iodine as an antimicrobial agent to a wound site or the skin. The purpose of presenting iodine in such a form is to reduce the staining and toxic (locally) properties inherent in the iodine molecule. Since most of the formulated iodine is tied up in the complex, the amount of "free" iodine available at any given instant is relatively small. Therefore, theoretically, the degree of irritation should be lessened. Indeed, the data submitted substantiate a reduced degree of iodine burn from the complex. In many cases, because the amount of "free" elemental iodine released from the complex is not enough to cause tissue burns, the area covered by it may safely be covered with adhesive tape or bandaged. This is a significant advantage for these iodine preparations over older iodine formulations, such as tincture of iodine. The concern of the Commissioner has been that this advantage of complexed iodine may also be its most serious disadvantage. The advantage of the iodophor is that the area can be treated and bandaged without irritation, while the serious disadvantage may be that actually there is less free iodine as an active antimicrobial. The Commissioner was presented no significant data about the "release" or dissociation of iodine from the complex. Additionally, the Commissioner is concerned about the lack of stability data of iodophor formulations.

The Commissioner is aware of the proposed mechanism, which has been described in U.S. Pat. 3,028,299 (Winicov, M. W. and W. Schmidt, "Germicidal Compositions and Methods for Preparing the Same," United States Patent No. 3,028,299, issued April 3, 1962), and the theory of the establishment of an equilibrium between free iodine and complexed iodine. The labeling for a given product states the amount of available or titratable iodine in the formulation. However, only a fraction is in the "free" elemental iodine form at the time of use. The concern of the Commissioner is the lack of data in the cases of actual use of the product which identifies the fraction that is "free". For example, once the "free" elemental iodine is bound to an organic load (in a wound, with serum, or on the skin), how rapidly is new elemental "free" iodine available from the complex? Does pH influence rate of release? Only preliminary data were presented to the Panel in the form of rapidity of titration with thiosulfate or ra-

padity of partitioning between two immiscible solvents. The Commissioner considers this form of data inadequate since it does not reflect actual conditions of use. For example, will the dissociation of iodine from the complex take place at the same rate in the presence of iodine bound to an organic load? No such data were submitted and before final classification of these iodophors for most applications can be made, such data are necessary.

Another area of concern for the Commissioner was the lack of stability data submitted for the several iodophor preparations. It is recognized that elemental iodine is a rather powerful oxidizing agent, as are all the halogens. It was suggested that some iodophors are not stable over a 2-year shelf life period. The Commissioner concludes that until data to the contrary are submitted, stability of iodophor products is sufficiently in question to require an expiration date not to exceed 2 years after manufacture and that stability data be submitted to the agency.

The Commissioner concludes that inadequate data on stability and availability of free iodine were presented for all applications to permit final classification of these surfactant iodophors at this time. Some data submitted suggest that with certain of the surfactant iodophors the volatile characteristics of iodine are not changed. In an occluded environment such formulations may corrode the tissue resulting in tissue burns. It was also suggested that all surface active agents cause hemolysis and tissue irritation and for this reason all surfactant-containing iodophors should be removed from soft tissue or surgical wounds prior to their closure. The Commissioner notes only a very small number of clinical studies with the surfactant iodophors which could shed light on these problems. The Commissioner therefore also concludes that surfactant iodophors must be studied to define retardation of wound healing before they are labeled as skin wound cleansers, skin antiseptics, and skin wound protectants. For all other product categories the following controlled studies should be conducted: blood levels of iodine (and iodide) and/or the carrier or complexing molecule following various types of usage of the product; systemic toxicity after absorption of the carrier molecule (animals only); and the target organ for toxicity from the carrier molecule.

As noted above, one of the primary concerns of the Commissioner is the influence of surfactant iodophors on rate of wound healing. Conflicting data were presented in the area of effect on wound healing. For example, several citations were submitted indicating little or no effect from the iodophor on rate of wound healing. In contrast to these, data were presented suggesting that certain nonsurfactant iodophors (povidone-iodine type) delay the rate of wound healing. In attempting to resolve this question, the Commissioner notes a paucity of controlled research that would define whether any delay in wound healing is due to iodine, carrier molecule, or the combination. He recommends that either the skin wound-healing procedure for rabbits or the procedure employing the use of hygrometry to assess wound repair on humans be carried out on iodine, the carrier molecule, and the combination (see testing guidelines).

Another primary area of concern to the Commissioner is the paucity of clinical evaluation data dealing with the claimed effectiveness of most of the surfactant iodophors. There were many in vitro tests reported, and the Commissioner is satisfied that, under the specific conditions of test for the in vitro evaluation, the specified iodophor had the stated antimicrobial effects. The Commissioner does feel, however, that clinical claims made from extension of the in vitro data were largely unwarranted in the absence of clinical data. The Commissioner will therefore require that appropriate controlled clinical studies for effectiveness of all product classes except skin wound cleanser and skin wound protectants be conducted on each surfactant iodophor in accordance with the testing guidelines below.

The Commissioner recognizes a danger in the use of iodophor and detergent (surfactant) preparations when there is contact with starch granules during a surgical procedure. Surgical gloves lubricated with powdered starch can cause idiopathic pathology after surgery. Such starch can absorb iodophors or detergents and the resultant complex can cause serosal adhesion and other undesirable effects in the body. The Commissioner will therefore require an appropriate label warning for products containing both povidone-iodine complex and surfactant-iodine complexes should they be classified as Category I in the monograph.

In specifying some shortcomings in the data submitted, the Commissioner does not mean to imply that a known hazard exists from these products. On the contrary, the Commissioner received enough toxicity data to convince him that there is no known hazard to the public from the use of these iodophors.

3. *Iodine complexed with nonsurfactant compounds.* The only example of this nonsurfactant type iodophor was povidone-iodine (polyvinyl pyrrolidone-iodine) complex. Some testimony was presented suggesting that povidone-iodine is a distinct chemical entity, while other testimony suggested that povidone-iodine is only a complex of polyvinyl pyrrolidone and iodine. In the absence of definitive data, the Commissioner is referring to povidone-iodine as a complex. Some evidence was presented that indicates iodine is released more slowly from povidone-iodine complex than from the surfactant-iodine complex. For skin antiseptics the Commissioner will require the same rate-of-release data in the presence of an organic load for the povidone-iodine complex as is required of the surfactant-iodine complex.

The Commissioner has reviewed the data available to the Panel as well as data submitted in the comments and concludes that the data proving the safety and effectiveness of povidone-iodine are still inadequate and the product must remain in Category III.

Data were presented that indicate that povidone-iodine preparations are used in volume on large burn areas, on vaginal mucosa, in large open wounds, and in abdominal surgery. Following such indiscriminate use, it was shown that some individuals exhibited altered protein bound iodine (PBI) levels and thyroid function. Therefore, the Commissioner cautions against such use in large volume or areas until more controlled research is conducted to show the conditions of use under which thyroid function would or would not be altered, and the amount of povidone-iodine required to induce alteration.

While reviewing the data submissions and comments to the Panel report, the Commissioner was concerned about label claims made without adequate supporting clinical effectiveness data. Statements implying "long-acting germicidal" activity or prolonged viricidal or sporicidal activity with iodine suggested clinical effectiveness over relatively long periods of time. Two questions relating to effectiveness of skin antiseptics arose from such implication: (1) What is the rate of release of "free" iodine from the complex in a clinical application and (2) what is the evidence of "germicidal" activity over a period of time in a clinical application? The Commissioner concludes that definitive research must be conducted to answer these questions as well as to define the limiting conditions for the antimicrobial activity of iodine, whether free or bound in an iodophor before povidone-iodine complex can be placed in Category I.

Reports have appeared in the literature which have indicated possible lymph node changes by circulating povidone-iodine. The Commissioner recognizes that certain molecular weights of povidone have been used as plasma expanders, which have caused the node changes. Povidone-iodine preparations have been used in large open wounds and in the abdominal cavity, but the Commissioner feels that inadequate data were made available to prove positively that such lymph node changes do not take place following such uses of povidone-iodine. The primary recommendation for additional work in this area is to show the extent of scavenging of residual povidone-iodine molecules by the reticuloendothelial system and possible lymph node involvement following use in abdominal cavities or in large wounds. As noted in paragraphs 71 and 72 above, in the event that povidone-iodine is classified as Category I and included in the monograph, it would need to carry a warning against use in deep or puncture wounds and a warning in professional labeling against use of this ingredient parenterally, use in the body cavities, and exposure of open surgical wounds to it. The Commissioner is convinced by the Panel report that there is little, if any, danger of

carcinogenesis from residual povidone-iodine molecules.

4. *Conclusions on iodophors.* The general deficiencies noted with the iodophors involve both safety and effectiveness, while the issues related to elemental iodine primarily involve safety questions of wound-healing delay. For iodophors, the question of iodine release from the complexed molecule, including rate of release and binding to other materials, as well as the influence of the release rate on effectiveness, must be resolved.

The stability of complexed iodine over time and with varying environmental conditions must be known and controlled so a stable product is marketed and effectiveness can be assured. Because of this stability problem, all topical antimicrobial products containing complexed iodine must bear an expiration date. The systemic absorption of topically applied iodine must be measured using the currently accepted assay procedures. In some cases, the toxicity of the carrier molecule has been only superficially characterized.

Neither the Commissioner nor the Panel was presented any data to show that iodine (elemental) or iodophors can be formulated into antimicrobial soaps. Accordingly, these ingredients are not generally recognized as safe or effective for such use (Category II).

F. QUATERNARY AMMONIUM COMPOUNDS

Since the first introduction in 1935 of quaternary ammonium salts ("quats") with surface active characteristics used as antimicrobial agents, there has been wide use and acceptance of these compounds as antiseptics and disinfectants. There has also been much controversy concerning their microbial spectrum, inactivation with incompatible materials, and potential hazard as a result of gram-negative contamination, particularly with *Pseudomonas*.

Quaternary ammonium compounds are cationic surface active agents. They can be differentiated from nonionic and anionic surface active agents in that they are essentially organically substituted ammonium compounds which can be characterized by the following general representation: $[R_1R_2NR_3R_4]^{(+)}X^{(-)}$. "R" represents a lipophilic group such as long chain hydrogen alkyl or aryl-alkyl radicals or other groups; "X" represents a negative ion such as a halide, sulfate or other radical; and "N" represents nitrogen.

The inherent nature of this type of molecular structure allows the synthesis of a large number of variants. The challenge has been met by the production of extremely large numbers of these compounds. The Commissioner has reviewed only three of these, and restricts his comments to those for which data were submitted: Benzalkonium chloride, benzelthonium chloride, and methyl benzethonium chloride. It should be understood, however, that these compounds have characteristics that are common to the whole class of quaternary ammonium compounds. While the microbial spectrum does not vary significantly among these compounds, an expanding list of new synthesized compounds could lead to a wider variation in the spectrum of microbes attacked. However, because only these three quaternary ammonium active ingredients were submitted to and reviewed by the Panel, all other quartenary ammonium compounds are not generally recognized as safe or effective unless and until appropriate petitions are received and approved modifying the monograph. Only holders of new drug applications may continue to market quaternary ammonium compounds other than benzalkonium chloride, benzethonium chloride, and methyl benzethonium chloride.

There is an interference action between cationic and anionic surface active agents with the result that these ionic types of compounds cannot be formulated together without inactivation of the germicidal activity of both compounds. In contrast, the nonionic compounds are often formulated with cationic "quats" in products known as germicidal detergents.

"Quats" and all surface antibacterials have been shown to affect membrane permeability. Indeed, this group of compounds has been called membrane-active. Many authors have recorded the loss or leakage of cell contents after exposure to "quats." Specific transport mechanisms may also be affected. "Quats" probably produce a generalized breakdown in the semipermeable characteristics of the membrane.

Gram-positive microorganisms are generally more susceptible to the effect of the "quats" than gram-negatives.

The "quats" are nonspecifically adsorbed to the cell membrane. In any case, the unprotected cell membrane is sensitive to the action of the "quats." Difference in sensitivity is conferred by access to the cell membranes.

This difference is probably due to the differences in the cell wall of gram-positive and gram-negative microorganisms. The adsorptive character of the cell wall probably determines the ability of the quaternary to reach and affect the cell membrane beneath the cell wall.

Early reports of the bactericidal activity of "quats" in low concentrations could not be supported when adequate neutralizing chemicals were added to the culture medium for testing antibacterial activity. In early tests, enough "quat" molecules adsorbed to the cells were carried over into the subculture medium to prevent the cells from growing when transferred to culture media. The meaning of the results of such tests was misjudged and misinterpreted during the early effectiveness testing of the "quats."

The gram-negative *Pseudomonas* species are frequently resistant to destruction by "quats." The lack of lethal activity of "quats" against *Mycobacterium tuberculosis* has been well established. The fungicidal activity of "quats" is generally less than against bacteria and only some of the newer "quats" show any significant antiviral activity. Tables listing the spectrum of "quats" against a variety of microorganisms are numerous.

The presence of organic materials substantially reduces the antimicrobial effectiveness of "quats." Their surface active nature permits easy adsorption on surfaces of even glass and plastic, and consequently, residues of "quats" may remain. In fact, the adsorption of "quats" onto the bacterial cell surface and subsequent carryover to the subculture medium in testing accounts for early exaggerated claims of effectiveness for "quats."

The cationic "quats" are inactivated by anionic compounds, soaps, Tween 80, and sodium lauryl sulfate as well as by certain metallic ions. Hard water and acidity also reduce the activity of the "quats." On the other hand, among newer "quats" synthesized there are some which are not adversely affected by hard water and acidity.

Because of their reported low toxicity and ease of use, especially with detergents, these compounds have been widely used for dipping solutions and "cold" instrument sterilization in hospitals. Organic material is commonly added to the solutions; and as a result of failure to clean materials or replace old solutions, added microorganisms are not inactivated and can grow and reproduce. Several serious outbreaks of gram-negative infection, as well as infections caused by other organisms, have been reported as a result of contaminated quaternary ammonium solutions.

Preservative ingredients can be added to quaternary ammonium salts to prevent the growth of gram-negative microorganisms, particularly *Pseudomonas*. Such a preservative system must be adequately challenged by effectiveness testing. The minimum acceptable standard for challenge testing of the preservative system and the chemical content would be the USP XIX Antimicrobial Preservative-Effectiveness Test (pp. 587–588) and the Antimicrobial Agents-Content Test (pp. 621–622).

The Commissioner is not seriously concerned with the safety of "quats" for "first-aid" uses, i.e., in skin wound cleansers, skin wound protectants, and skin antiseptics. However, before "quats" in general can be finally classified for such uses, the following minor issues must be resolved: delay of skin wound repair, contact dermatitis, and sensitivity to "quats." Data on the effectiveness of quats for these uses must also be developed. The three "quats" for which data were submitted have, however, had these questions sufficiently resolved to be classified in Category I for use in skin wound cleansers.

While human systemic absorption and toxicity after topical application cannot be precisely established based on a review of the scientific literature or submitted data, the systemic toxicity of "quats" in animals is low. The LD_{50} and chronic oral study values in several animal species are reported. The toxicity reported is indicative of and reflects the surfactant nature of the molecule. The

"use dilution" for the "quats" is usually about 1/750 for topical application.

Further, even though specific absorption and systemic levels in humans have not been reported for the three "quats" reviewed, considering the concentrations applied, and extrapolating from animal studies, toxic effects at use levels would be unlikely.

The irritating nature of quaternary compounds on the skin, mucous membranes, and in the eye have been reported extensively. The degree of irritation is dependent on concentration and/or occlusion. However, there is little irritation potential with the use concentrations.

Various reports of toxicity related to the detergent nature of these compounds have been published. Two authors reported that repeated application of 1 percent benzethonium chloride to the skin caused damage with cellular degeneration. "Quats" have been shown to alter the permeability of the human skin to sodium and potassium ions and to cause enhanced percutaneous absorption. Also, occasional reports of nonallergic and allergic contact dermatitis have been made in several reports.

Necrotic ulceration has occurred where detergent creams containing "quats" have been applied to moist areas of the skin of the genitals and buttocks under occlusion.

A number of published articles that deal with the toxicity of the specific "quats" have been reviewed. References to sensitivity and contact dermatitis produced with "quats" have been reported.

One aspect of the result of the use of "quats" deals with both effectiveness and safety. Over the years since their introduction, the variety and frequency of their use have increased. Several reports indicate systemic infections by *Pseudomonas aeruginosa* and other gram-negative bacteria resulting from contamination of detergent fluids in which surgical instruments had been stored. These untoward episodes are not all necessarily due to inherent properties of the "quats," but can result from misuse, contamination with neutralizing substances, and improper conditions of storage.

The Commissioner is aware that use or misuse of quaternary ammonium compounds in health-care facility environments has in certain instances been associated with outbreak of *Pseudomonas* and other gram-negative bacterial infections. Such modifications in microbial environments must be studied. In addition, until such studies have been reviewed by the agency the warning will have to appear on professional labeling for all quaternary ammonium compounds intended for use in health-care facility environments that misuse or overuse may lead to *Pseudomonas* or other gram-negative pathogen overgrowth with attendant health risk to debilitated patients.

The Commissioner concludes that the effectiveness of the "quats" appears to be limited and that their effects in vivo on either resident cutaneous flora or on potentially pathogenic transients on the skin have not been clearly demonstrated. This conclusion is based on the relevant factors which follow.

While the growth of *Staphylococcus aureus* and certain other gram-positive bacteria is inhibited by low concentrations of the "quats" in vitro, their reaction to these substances within the cutaneous ecosystem has not received sufficient attention. Since it has been shown that "quats" are rapidly adsorbed to proteins and to cotton fibers and their germicidal activity is reduced in the presence of serum and soap, their effectiveness on the skin or in superficial wounds is much less than would appear from results obtained with in vitro procedures.

Many gram-negative bacteria are resistant to the germicidal action of "quats," and some strains of *Pseudomonas* can survive and mutiply in aqueous solutions of these substances. Such strains may be resistant to related preparations. Strains of the same species can also vary in their sensitivity to the "quats," and this attribute can change as a result of artificial culture. In vitro testing of a series of strains recently isolated from human infections and other appropriate habitats must be undertaken before the germicidal effects of the "quats" on gram-negative species can be satisfactorily assessed.

Mycobacterium tuberculosis, some species of *Clostridia,* most dermatophytes, and many viruses are not inactivated by the "quats." There are few reports on the in vitro or in vivo susceptibility of pathogenic fungi or protozoa to "quats."

Various reports show that the application of "quats" to the skin reduces both the bacterial count on hands and in the axilla with subsequent reduction of body odor. However, the Commissioner concludes that since the three quaternary ammonium compounds cannot be formulated into antimicrobial soaps, they are not generally recgonized as safe or effective for such use.

The three quaternary compounds reviewed by the Commissioner have been widely used for many years. Further safety data need only be developed where appropriate for particular product classes as set forth above in this discussion. In addition, the in vivo effectiveness of these ingredients for the product categories other than skin wound cleanser and antimicrobial soap needs to be evaluated as set forth in the testing guidelines below, including the use of specific neutralizers.

G. PHENOL 1.5 PERCENT OR LESS IN AQUEOUS/ALCOHOLIC SOLUTION

Lister first demonstrated the usefulness of carbolic acid (phenol) as a germicide in the surgical theater in 1867. Although it has been used since then, the topical use in particular has declined in recent years with the availability of new antimicrobials. Its microbicidal mode of action is as a protein denaturant. An easily dissociated complex of the phenol molecule and protein is formed. This complex formation permits the penetration of phenol through intact or abraded skin, mucous membranes or subcutaneous tissues with which it comes in contact. Phenol also may gain access to the pulmonary circulation through inhalation of its vapors. Many of the toxic effects discussed occur when phenol is absorbed at levels of 1.5 percent or less. However, toxic effects are more serious at concentrations greater than 1.5 percent. (See discussion of phenol greater than 1.5 percent.)

Although phenol is no longer a significantly used antimicrobial, it is still formulated in topical products, and there is a large body of literature concerning its effectiveness. Phenol was widely used and accepted as an antiseptic when little else was available, and its use is certainly historically important. However, it is now obvious that the level of phenol required in a formulation to be effective is frequently so high that it cannot be used safely on the skin.

Phenol can be bacteriostatic or bactericidal depending on the concentration. Phenol is not sporicidal.

The mechanism of action on the microbial cell is very likely the disruption of the cell wall and precipitation of the cellular proteins.

Because phenols have a high oil/water partition coefficient (tendency for phenol to remain in the oil phase), the antimicrobial activity may be decreased in the presence of excess oil or fats. Since many phenol products are formulated as ointments or creams, in vivo studies must be conducted to show the antimicrobial effectiveness of phenol in these formulations. In addition, many of the reported effectiveness tests for phenol published in the literature and/or submitted to the OTC Panel were carried out before the development and use of neutralizers in antiseptic testing.

Phenol is a classic example of a chemical which is metabolized and eliminated from the body by glucuronide conjugation in the liver. This mechanism may be deficient in young animals and human infants. The Commissioner finds that inadequate data concerning elimination and toxicity in young animals were submitted. The Commissioner concludes that adequate research in young animals with blocked formation or unavailable glucuronide systems be conducted in order to define the toxicity potential for human infants. Since the liver is considered the major organ for conjugation, the effect of inadequate or impaired liver function on elimination and toxicity should also be determined.

Therefore, the Commissioner recommends that unless such studies as described above are conducted within 1 year following publication of the final monograph in the FEDERAL REGISTER this ingredient should not be used on infants. The label for the preparation containing the ingredient would need to state: "Not to be used on infants under 6 months of age."

The Commissioner notes that the Panel reviewed a published report that doses of

phenol above 5 percent act as a tumor promoter in mice when applied topically (Boutwell, R. K. and D. K. Bosch, "The Tumor-promoting Action of Phenol and Related Compounds for Mouse Skin," *Cancer Research*, 19:413–424, 1959), and that the Panel concluded that carcinogenicity studies should be done to determine whether in fact phenol itself may have any carcinogenic potential. The Panel also said that data on the teratogenic and mutagenic potential of phenol should be developed.

The Commissioner recognizes that the accepted protocol for determining the potential for the carcinogenicity or cocarcinogenicity (tumor promotion) of any drug is the National Cancer Institute (NCI) standard bioassay program. Phenol has been included in this program, but the results are not yet available. The Commissioner will carefully review the results of the NCI study and will determine at that time whether any regulatory action is appropriate. The Commissioner concludes that, since no evidence of teratogenicity or mutagenicity was presented to and reviewed by the Panel, and since there are no reports in the many years of experience with phenol suggesting that it has a teratogenic or mutagenic potential, mutagenicity and teratogenicity studies are not required.

The Commissioner concludes that the total concentration of phenol in powders and in aqueous, alcoholic, or oil formulations be restricted to less than 1.5 percent. When camphor is used with phenol in an oil formulation, the concentration of phenol should be no more than 5 percent. Chemicals with phenol activity, such as sodium phenolate and secondary-amyltricresols, should be considered as phenol in the calculation of the total phenol in any formulation. The amount of phenol available as an antimicrobial will, of course, depend upon the particular formulation and the amount of phenol in a free state. The Commissioner further concludes that phenol may be used as an inactive ingredient for its aromatic characteristics in formulations, but at a concentration of less than 0.5 percent of phenol in a free state.

It seems apparent that even with phenol's long history of use, the Commissioner must now recognize that the levels at which phenol in aqueous and alcoholic formulations is effective topically are also the levels at which topical and systemic toxicity may occur, even though severity of toxicity is dependent on concentration. The fact that these two elements converge has made it necessary for the Commissioner to limit the concentration which may be marketed while testing for safety is concomitantly performed to less than 1.5 percent. Because the Commissioner is aware of rather severe toxicity with the use of phenol in animals and man, concentrations greater than 1.5 percent are not generally recognized as safe. (See discussion of phenol greater than 1.5 percent.) Even though the effects of phenol toxicity at lower concentrations are similar, the severity is dependent on the concentration. It is the Commissioner's view that the demonstration of effectiveness at 1.5 percent or less may be exceedingly difficult but that the use of this concentration does not present a known hazard to the consumer. The toxicity of phenol has been extensively described. The major lack of data is in vivo efficacy studies with concentration at 1.5 percent or less. In vivo studies performed with modern testing and skin sampling procedures, including the use of neutralizers, are required.

Because of the reports of local and systemic toxicity after the use of phenol-containing products covered with bandages over large areas of the body, the use of phenol is restricted to small areas of the skin, and occlusive dressings, bandages, or diapers in any form should not be used. Phenol-containing preparations should not be used for the treatment of diaper rash. The label should state: "Warning: Do not use for diaper rash or over large areas of the body or cover the treated area with a bandage or dressings". Because of this safety consideration, this warning will be required to appear on all phenol-containing preparations within the purview of this document at the time labeling required in the monograph must appear on OTC antimicrobial products.

H. PARA-CHLORO-META-XYLENOL

Very little information was submitted to the Panel with regard to para-chloro-meta-xylenol (PCMX). Only a few acute oral and inhalation studies were submitted. These studies do not indicate a high degree of acute toxicity with an oral LD_{50} of greater than 3 gm/kg in rats.

However, because the information that could be obtained from subchronic dosing by various routes of application, determination of target organ, dermal and mucosal absorption, and metabolic studies are not available, an evaluation of the safety of this chemical in a topical preparation could not be made. There were two reports of contact dermatitis associated with PCMX. In addition, information is not available regarding the effects of para-chloro-meta-xylenol on wound healing. The Commissioner notes that the Panel did not review any studies evaluating the carcinogenic, mutagenic, or teratogenic potential of PCMX, and that to the Panel's knowledge no such studies had ever been performed on PCMX.

It has been reported that PCMX is metabolized by glucuronide and sulfate conjugation. Due to the reported deficiency of metabolic conjugating mechanisms in infants, the Commissioner concludes that toxicological safety evaluation of PCMX should include studies to demonstrate safety in animals deficient in these detoxification mechanisms. Since the liver is considered the major organ for conjugation, the effect of impaired liver function on elimination and toxicity would be important.

Therefore, the Commissioner concludes that unless such studies as described above are conducted within 1 year following publication of the final monograph in the FEDERAL REGISTER this ingredient should not be used on infants. The label for a preparation containing the ingredient would need to state: "Not to be used on infants under 6 months of age".

PCMX is a halogen substituted phenol compound. Many of the comments made for the effectiveness testing of phenol apply here. Halogen substitution increases the antimicrobial activity of phenol derivatives. The halogen in the para-position to the hydroxy group is considered the most effective substitution. Thus, the indications are that this compound would show good in vitro activity. Very little information about the in vivo activity on the skin is published or was submitted to FDA for review. At least one report, using a serial washing technique, indicated only a slight effect on resident bacterial flora of the skin. Another study reported approximately a 70 percent reduction in microbial count of the flora of the hands after 10 days of use.

PCMX is primarily active against gram-positive organisms with activity against gram-negative microorganisms in vitro. Fungicidal activity in vitro is also reported. The phenol coefficient is reported to be around 40, but the results vary.

Claims for broad spectrum activity have been made for this compound; however, the Commissioner finds that inadequate effectiveness data were submitted. Many studies were old and not performed with modern antiseptic testing procedures. The Commissioner concludes that effectiveness testing both in vitro and in vivo should be done in accordance with the Guidelines elsewhere in this document.

Only the most superficial toxicity data in animals were submitted to and reviewed by the Panel. The Commissioner concurs with the Panel that toxicity in rodent and nonrodent species, substantivity, blood levels, distribution and metabolism as well as any subsequent systemic absorption studies must be characterized before this ingredient can be considered for placement in Category I.

Although additional data were submitted after publication of the Panel's report, the Commissioner has reviewed these data and finds that they are not sufficient to permit classification of PCMX in Category I. The additional material consists of routine toxicity tests and some in vitro testing. The techniques used and the level of sophistication displayed do not meet the Guidelines discussed elsewhere in this document.

The degree of absorption of PCMX following topical administration has not been established. The target organ for PCMX toxicity in animals also remains unidentified and should be shown in a long-term animal toxicity study. Therefore, the Commissioner concludes that those studies described above should be conducted within 2 years following publication of the final monograph in the FEDERAL REGISTER. PCMX should not be used in infants until these studies have been completed and evaluated. In vitro and vivo efficacy studies with up to date sampling techniques, including the use of neutralizers, are also required. The

Commissioner disagrees with the Panel that carcinogenicity, mutagenicity, or teratogenicity studies must be completed. The Commissioner concludes that, in the absence of any data suggesting that PCMX has any carcinogenic, mutagenic, or teratogenic potential, testing for these properties should not be required.

I. HEXYLRESORCINOL

The Commissioner has reviewed the Panel's report as well as other data regarding the safety and effectiveness of hexylresorcinol and has determined that though this ingredient is safe, he has insufficient information regarding its effectiveness to place it in Category I.

Hexylresorcinol has a history of use as an oral anthelminthic in humans. In these cases the dose used in children has been 600 to 800 mg and in adults 1,000 mg, without systemic toxicity. However, irritation and ulceration of the oral and gastrointestinal mucosa have been reported from these high doses. The few animal toxicity studies submitted as summaries indicate a low order of toxicity.

During its long history of use, there have been a few reports of dermatitis and allergic reactions following the topical application of hexylresorcinol to skin and of irritation of the oral mucosa from the use of cough drops and toothpaste containing hexylresorcinol. The Commissioner concludes that hexylresorcinol does not present a known hazard to the general public from use as a topical preparation.

Data have been submitted demonstrating in vitro effectiveness using techniques available some years ago. Neutralizers for antiseptic testing were not in general use at the time these studies were performed and their use was often ignored. Nevertheless, that effectiveness data looked very promising.

The Commissioner has reviewed rather extensive reports of the oral administration of hexylrescorcinol to humans with other accompanying animal toxicity data and has concluded that topical application, even where absorption might occur at high levels, is safe. The area in which data are lacking concerns the in vitro and in vivo effectiveness of the ingredient and of formulations containing it. Appropriate effectiveness data for the different product classes must be generated using testing procedures and skin-sampling techniques, including the use of neutralizers as set forth in the testing guidelines.

J. TRIPLE DYE

The Commissioner has reviewed the safety and effectiveness of the combination of antibacterial dyes (crystal violet, 2.29 gm, brilliant green, 2.29 gm, and proflavine hemisulfate, 1.14 gm and sufficient water to make 1,000 ml) known as triple dye for the treatment of the umbilicus prior to the availability of hexachlorophene for this purpose. He has also reviewed its recent use in the prevention of staphylococcal colonization of neonates as a possible replacement for hexachlorophene. He concludes that the evidence indicates that a single application of triple dye to the umbilicus is effective in the reduction of staphylococcal colonization in infants in the hospital nursery. However, additional safety data, including the degree of percutaneous absorption and concomitant toxicity of the combination, are required.

Additional effectiveness data are needed to determine the duration of protection following a single application of dye. The difficulty in establishing effectiveness by skin sampling for staphylococcal colonization is increased by the presence of small quantities of transferred dye in the culture medium used to isolate staphylococci and must be considered in further tests of effectiveness.

It is the opinion of the Commissioner that the data reviewed were not sufficient to permit final classification of triple dye.

The application of triple dye to the umbilicus is a potential replacement for hexachlorophene bathing of infants in the nursery to reduce staphylococcal colonization. Further data on the absorption and possible carcinogenicity of the dye ingredients should be generated before triple dye can be placed in Category I for this limited indication.

K. COMBINATION ANTIMICROBIAL PRODUCTS

The Commissioner has reviewed data on antimicrobial bar soaps containing a combination of active ingredients. One of these, containing triclocarban and cloflucarban, is classified in Category III. The other, containing tribromsalan and triclosan, is placed in Category II. No information on the safety and effectiveness of other combinations of ingredients was received. Therefore, for lack of data, they are not generally recognized as safe or effective. Conditions possibly exist where the benefit-to-risk ratio is such that their use may be valuable, if not necessary. However, such combination antimicrobial agents should not be available for over-the-counter use until sufficient safety and effectiveness data are submitted. In addition, information on a third combination, containing quaternary ammonium compounds, was submitted during the comment period. Data contained in the submission were sufficient to show that the combination does not pose a health risk of any kind, but insufficient to show whether the individual ingredients or the combination is generally recognized as safe and effective. Accordingly, that combination is placed in Category III.

For all combinations the level of each antimicrobial ingredient in the combination must make a contribution to the claimed effect for the product. The total amount of individual antimicrobial ingredients, in combination, should result in an effect that is at least equal to that achieved when any one of the individual ingredients is used alone at the same total concentration without significantly reducing safety. In some instances the Commissioner has established maximum dose levels of an antimicrobial when used alone. If such antimicrobials are placed in combinations, no individual antimicrobial in the combination may exceed the dose level approved by the Commissioner.

The Commissioner believes that antimicrobial agents are somewhat different from combinations of other OTC ingredients in that they act upon a foreign entity, the microorganism, rather than the host. In combinations of nonantimicrobial ingredients, the advantage of the combination may be that therapeutic activity is obtained at lower dosages for each component ingredient, whereas there can be no contribution to effectiveness of an antimicrobial ingredient by combining it with antimicrobial ingredients having identical bactericidal, virocidal, and fungicidal properties. Consequently, the Commissioner concludes that a rational combination of antimicrobials should have one of the following purposes: expansion of the microbial spectrum relevant to the product class for which the combination is intended, reduction of the toxicity of one or both of the ingredients, or a synergistic effect.

Furthermore, when two or more ingredients are combined as antimicrobial soaps, toxicity data must be available to show that the metabolism, excretion, or target organ toxicity are not enhanced or synergistically affected by the combination, for example, through the metabolism or excretion of one of the ingredients. When two or more antimicrobial ingredients are combined for the other product class, data must be available to show no decrease in safety.

IV. FINAL TESTING GUIDELINES FOR SAFETY AND EFFECTIVENESS OF OTC TOPICAL ANTIMICROBIALS

A. INTRODUCTION

As noted above, the Commissioner adopts the findings of the Panel for Category III testing guidelines by restating them in this document. However, these guidelines have been extensively modified to incorporate new data, new testing approaches, and to reflect more accurately the needs of the agency in determining general recognition. The Panel's findings have also been modified for clarity, regulatory accuracy, and to delete gratuitous or unsupported statements. In addition, the Commissioner's agreement with comments that suggested modification of the Panel's findings are reflected in the Commissioner's version of this section.

Important substantive modifications made by the Commissioner are: 1. Addition of the safety factor calculations discussion contained in the Panel report (39 FR 33112);

2. Modification of the topical safety discussion in section A.1 (39 FR 33135), relating to the effect of an antimicrobial ingredient on shifts in the body's normal microbial flora, to require the shift not to result in evident pathological changes;

3. Modification of the systemic safety discussion in section A.2. (39 FR 33135) to: a. Delete the requirement of development of chemical analysis and/or bioassay techniques for detection of the chemical or its metabolites in biological tissues and secretions;

b. Require determination of blood levels reaching plateau and other long-term pharmacologic effects; and

c. Delete the requirement of determining metabolic fate of an ingredient as it is metabolized in the body. Such a requirement is far beyond the intended scope of testing guidelines for general recognition of safety and effectiveness.

4. Modification of the in vitro effectiveness testing requirements in section B.1 (39 FR 33136) to: a. Accept the concept that reduction of normal microbial flora, both resident and transient, is beneficial;

b. Set limits of microbial flora reduction needed before certain claims can be made, e.g., 1 $\log_{10}$ reduction for antimicrobial soap effectiveness; and

c. Set forth those organisms upon which these antimicrobials must be tested.

5. Modification of the in vivo effectiveness testing requirements in section B.2. (39 FR 33136) to: a. Require a determination of the minimum concentrations of active ingredients required to produce the claimed effect for particular product classes; and

b. Delete the Quinn Handwashing Test for antimicrobial soap effectiveness.

6. Set forth several additional testing protocols including: a. Animal and human tests for determining delay in wound healing for "first-aid" product classes;

b. A test for demonstration of the ability of a skin wound protectant to act as a barrier against further contamination with microorganisms; and

c. A test for determining that a skin wound protectant does not favor growth of microorganism.

7. Inclusion of U.S.P. and CTFA tests, with modifications, for determination of the effectiveness of antimicrobial ingredients as preservatives.

The Commissioner considers these testing guidelines to be final, subject to modification upon a properly supported request. These guidelines, and future modifications thereto, will be available in the office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857. No further changes in these guidelines will be published in the FEDERAL REGISTER. However, notification of amendments to the guidelines will appear as a notice in the FEDERAL REGISTER pursuant to § 10.90 (b) (5) of the agency's regulations on Administrative practices and Procedures (21 CFR 10.90(b)(5), formerly § 2.20(b) (5) prior to recodification published in the FEDERAL REGISTER of March 22, 1977 (42 FR 15553)).

After review of the data submitted for antimicrobial ingredients in soaps, surgical scrubs, skin washes, skin cleansers, and first-aid products submitted to and considered by the Panel, the Commissioner has developed the following guidelines for safety and effectiveness studies. These guidelines, which must satisfy the requirements for adequate and well-controlled studies as specified in 21 CFR 314.111(a)(5)(ii), may be followed to develop data for specific ingredients where the information does not currently exist.

The Commissioner recognizes that antimicrobial use ranges from total body exposure to application on small areas of the body. Such use may extend from daily and repeated, to intermittent and occasional application. The Commissioner also recognizes that the list of products may include solids, liquids, creams, powders, and aerosols formulated with various chemical excipients. Those manufacturers or distributors who desire to move Category III ingredients or combinations into Category I should select from the guidelines those tests appropriate for their type of product and its intended use. They should be prepared to explain and justify their test selections. Test data submissions will not be required beyond those which the Commissioner has stated are required in the Category III discussion above. For example, the Commissioner will not require long-term toxicity studies for product classes of the short-term or single-use variety, such as the "first-aid" product classes.

The Commissioner recognizes that there may be honest disagreement among scientists about the most appropriate design of a protocol for a test to provide data on which a final determination of general recognition of safety and effectiveness can reasonably be made. The Commissioner also recognizes that some of the studies are in areas or require procdures for which precedents are not common and for which agency guidance is necessary. In these events, conferences with expert consultants and with representatives of the Food and Drug Administration are recommended and requests for modification of these guidelines will be considered. Such requests should be submitted to the agency. All such submissions shall be mailed or delivered in person to the office of the Hearing Clerk (HFC–20), Food and Drug Administration, room 4–65, 5600 Fishers Lane, Rockville, MD 20857 and identified with Docket No. 75N–0183.

B. TESTING GUIDELINES

Since topical antimicrobial products frequently have a considerable placebo effect, there should be some demonstration that the formulated product is better than the vehicle alone. Testing of the complete formulation for Category III ingredients for effectiveness and safety is necessary to judge the importance of the vehicle in the release of the active ingredient as well as the influence of formulation on aspects of effectiveness and safety. Once an ingredient is placed in Category I for a particular product class, no further final product formulation data need be submitted to the agency. However, manufacturers should have data on file to show that the vehicles and other inactive ingredients used in the formulation of the various antimicrobial products classes included in the monograph do not materially affect either the safety or the effectiveness of Category I active ingredients.

1. Safety—Tests below should be performed on suitable animals and then on humans when applicable, appropriate, and ethically feasible.

The following tests should be performed for all product classes, except skin wound cleansers without antimicrobials, unless otherwise specified, using the active ingredient alone and in the final complete formulation to judge the effect of vehicle in the release of active ingredient(s).

a. *Safety factor calculations.* The Commissioner consludes that a minimum of a 100-fold safety factor should apply to the exposure dose for ingredients labeled for repeated daily use. At present this limit is applied to antimicrobial soaps, health-care personnel handwashes, and surgical hand scrubs. The Commissioner has reviewed the Panel's discussion of safety factors for topically applied antimicrobial agents (39 FR 33112–33114). He fully concurs with the conclusions reached by the Panel and adopts them as part of the testing guidelines. However, he will not restate the whole discussion on safety factors, only the methods for calculating such factors.

Calculations were made from data presented for various ingredients. Toxicological studies, where appropriate, should contain applicable administered doses, achieved blood levels, and observed pathological alterations in the same study and the same species. The calculations presented here are hypothetical, show the assumptions made, and are intended to explain the method. They are as follows:

(1) Expected no-effect dose level in man: Determine the lowest toxic effect and the highest no-effect dose in mg/kg topically applied in an animal species. (If an effect cannot be determined in a topical application, the oral route of administration should be employed.) Take the highest no-effect dose in that animal species and calculate the absolute dose. From the absolute dose the multiplication can be made with the factor given for the specific animal used in the test and this, then, is the dose level at which no-effect might also be expected in man.

(2) Expected blood level from product use in man: Assume a bar soap with 3 percent active antimicrobial is used for one bath per day. Assume that 7 gm of soap are used in one bath. This would give an exposure of 0.21 gm, or 210 mg per bath of active ingredient. Assume retention of all 210 mg active ingredient on the skin (there is very little firm data presently available on the amount of antimicrobial retained on the skin after exposure). If 3 percent of the applied active ingredient is absorbed into the blood stream, the dose per bath would be:

$0.03 \times 210.0 \text{ mg} = 6.30 \text{ mg}$ active ingredient absorbed.

If the assumption is made that the total dose is immediately absorbed, the dose distributed in the blood of a 70 kg human would be:

$$\frac{6.30 \text{ mg}}{5{,}000 \text{ ml blood/70 kg human}} = 1.26 \text{ mcg active ingredient per ml of blood.}$$

The assumption is made here that the amount of chemical presented to the individual in a single bath is all retained on the skin and absorbed and distributed in the blood, giving a blood level of 1.26 mcg/ml.

As a further example, assuming retention of 0.5 mcg of active ingredient per sq cm of skin and that the product is to be used over the entire skin area, as in a bar of soap, the total dose retained would be 9.25 mg over the entire body. The calculation would be 0.5 mcg per sq cm × 18,500 sq cm of skin (based on a 70 kg, 5'10" human). Assuming, for this case, a 10 percent absorption:

$$9.25 \text{ mg} \times 0.10 = 0.93 \text{ mg dose per bath}$$

If the assumption is also made that the total dose is immediately absorbed, the dose distributed in the blood of a 70 kg human would be:

$$\frac{0.93 \text{ mg}}{5{,}000 \text{ ml blood/70 kg human}} = 0.18 \text{ mcg active ingredient per ml of blood.}$$

Safety factors were calculated using the available evidence. For the specific calculations, see the individual ingredient statements.

These two hypothetical calculations using known facts with stated assumption are examples of the type of safety factor calculations considered by the Commissioner. In this calculation, the information required is the retention of the chemical by the skin after exposure. The missing information here is the absorption-excretion kinetics for that chemical.

A direct comparison can be made, and thus a safety factor can be estimated, by a comparison of the calculated human blood level with the blood level in animals, if known. A comparison of the dose where there is no effect in animals translated to the dose in which no effect may be expected in humans against the hypothetical dose to which a person is exposed from the use of a product containing the ingredient can be made if blood level data are not available.

It must be stressed again that the best calcualtions and judgments are made when all of the pertinent data are available and frequent assumptions do not have to be made. The variety of calculations presented to the Panel and then to the Commissioner are based on assumptions because the data are not available. Subsequent to the publication of the Panel report data were received on the absorption of a radioactively labeled triclocarban soap formation applied in a shower (see paragraph 74 above). These data were remarkably close to the hypothetical calculations of the Panel.

If the safety factor is extrapolated from an animal species to man, considering surface area, the highest no-effect dose should be used for the multiplier. In the absence of complete data, a 100-fold safety factor should be applied when translating the animal highest no-effect dose to man.

The ideal situation would occur where enough animal data have been collected to construct a dose response curve with concurrent blood levels so that analysis for threshold effect and safe level estimation for the animal can be made.

b. *Topical (skin).* Determine: (1) Primary irritation potential following acute and subacute exposure. Special attention devoted to eyes, mucous membranes, and genitalia.

(2) Allergic contact dermatitis potential following acute and subacute exposure.

(3) Photosensitivity potential (phototoxic and photoallergenic). The appropriate age group would be males over 40 since the reported incidence of photoallergy is highest in this group.

(4) Effect on wound healing (only for skin antiseptic, skin wound cleanser, skin wound protectant, and patient preoperative skin preparation).

(5) Effect on skin pigmentation. (This observation can be made concomitant with photopatch testing to determine photosensitivity potential.)

(6) Effect on total skin flora to ensure no detrimental overgrowth of a particular bacterial or fungal species that results in evident pathology.

(7) Substantivity, accumulation, or persistence in or on the skin. Although several product classes are single use or very short-term use type products, e.g., patient preoperative skin preparation, this requirement for all product classes will help to assure safety for more long-term abusive use, e.g., daily use of a patient preoperative skin preparation for a long period.

c. *Systemic.* Determine: (1) Degree of absorption (and subsequent blood level) through intact and abraded (damaged, diseased) skin and mucous membrane after single and multiple exposures. Testing to determine plateauing of blood levels and other pharmacologic effects that may take sometime to be evident should be performed. If the product is an aerosol, adequate inhalation studies should be conducted.

(2) The target organ(s) for toxicty effects via oral, topical and/or parenteral routes. Relate toxicity to blood levels of ingredient. Determine the "no-effect" and "effect" level in the same species and in the same study.

(3) Analytical chemical techniques must be utilized to determine concentrations of ingredients in the blood. This permits correlation of the topically applied dose to blood levels and any resultant pathological alterations.

(4) The LD_{50} obtained by the Wilcox-Litchfield method or other appropriate methods.

(5) Tissue distribution, metabolic rates, and rate and routes of excretion. For purposes of this testing procedure, the Commissioner defines metabolic rate as the time frame within which an active ingredient seems to disappear as it is metabolically modified.

(6) Teratogenic, mutagenic, carcinogenic, and reproductive effects. It is not necessary to conduct such studies with the marketed product where adequate data are available on the active ingredient alone.

2. *Effectiveness.* The Commissioner accepts the proposition that in the definition and/or historical use of all product categories except skin antiseptics, the reduction of the normal flora, both transient and resident, has been sufficiently supported to be considered a benefit. The only determination that remains, therefore, is how much of a reduction in microbial flora will be required to permit claims for the various product classes.

The Commissioner concludes that claims of effectiveness of antimicrobials as deodorants will be accepted if they are based on correlation between direct demonstration of odor reduction and a reduction in total microbial count of one log (1 $\log_{10}$), or by inhibition of microbial species shown to be responsible for odor production. The Commissioner notes that he has as of this date been unable to describe a specific protocol to prove effectiveness of antimicrobial ingredients as skin antiseptics. He will therefore accept suggested protocols and modify the testing guideline for this product class in the future.

Since product categories which did not exist previously have been defined, there has been a need to develop adequate testing procedures in some of these new areas, particularly in vivo testing procedures. The guidelines that follow are designed as an outline of procedures that the Commissioner believes will characterize the effectiveness of an antimicrobial ingredient for each of these product categories.

a. *In vitro testing.* The following tests should be performed for all product classes (except skin wound cleansers without antimicrobial ingredients) unless otherwise specified.

(1) Determine the antimicrobial spectrum of the chemical(s) alone and in its final formulation using both standard cultures and recently isolated strains of each species. Cultures representing normal skin flora and skin pathogens should be selected as set forth below.

Develop techniques for adequate neutralization of the active ingredient, before testing its antimicrobial spectrum. Ensure that the neutralizer is not toxic to the test organisms.

The following outline has been prepared to serve as a basic guide for the in vitro characterization of the activity of an antimicrobial ingredient:

(2) Determine the minimal inhibitory concentration (MIC) under standard conditions against standard organisms with known phenol resistance and susceptibilities to other antimicrobial chemicals.

A series of recently isolated mesophilic strains, including members of the normal flora and cutaneous pathogens (100 isolates), should be selected.

The list of organisms to be tested are those considered to exist in the "normal environment" (normal skin flora or pathogens likely to be found in a minor wound). The Commissioner requires that they be used in testing unless data can be presented to the agency that other organisms are equally representative of those found in the "normal environment." There must be no claims, either direct or by implication, that a product

has any activity against an organism, or that it reduces the number of organisms, for which it has not been tested.

The Commissioner notes that, if there is some reasonable scientific indication that the activity of an ingredient will affect the microbial flora, and thereby causes a rise in the fungus or virus level that might result in greater harm, then further testing will be required.

Representatives of the following groups should be included (note: special media and/or environmental conditions may be required):

(i) Staphylococci-5 groups.

(ii) Micrococci.

(iii) Pyogenic *Streptococci* (Groups A, C, and D should be included).

(iv) Diphtheroids-Lipophilic, Anaerobic (Propionibacterium).

(v) Gram-negative enteric bacilli:

(*a*) *Escherichia, Enterobacter, Klebsiella, Proteus,* and *Serratia.*

(*b*) *Pseudomonas aeruginosa* and *Pseudomonas* species.

(vi) Yeast—*Candida albicans, Candida parapsilosis.*

(vii) Selected Filamentous Dermatophytic species. (Required only for health-care personnel handwash, surgical hand scrub, skin wound cleanser, skin wound protectant, and skin antiseptic.)

(3) Determine possible development of resistance to the chemical. Sublethal levels of the active ingredient(s) can be incorporated into the culture medium for an extended series of exposures. Use standard methods to determine the emergence of resistance.

(4) Data substantiating antimicrobial action by standard procedures, such as the Sykes-Kelsey procedure, phenol coefficient, or others where applicable, should be provided. It would be advisable to include in the in vitro test a chemical(s) with recognized antimicrobial activity, for purposes of comparison.

b. *In vivo.* (1) The following tests, approximating use conditions for the clinical evaluation of each label claim of the formulated product, should be carried out for the product classes specified:

(i) For all product classes, a determination should be made of the quantitative and qualitative estimation of reduction of the skin flora, both transient and resident through the skin-stripping or cup-scrubbing techniques (discussed below in the specific protocols). All product classes should include not only alteration in total numbers of microorganisms, but qualitative changes (such as dominance of a different type or change in antimicrobial resistance) in the residual cutaneous populations. For antimicrobial soaps only, sampling should be carried out on microbial communities in several different areas of the body, such as axilla, groin, feet and hands, along with a showing of a 1 $\log_{10}$ reduction of skin flora or a significant inhibition of microbial species shown to be responsible for odor production.

(ii) Glove juice procedure (surgical hand scrubs only).

(iii) Antimicrobial soap effectiveness (odor reduction)—Cade handwashing test (antimicrobial soap only).

(iv) Handwash effectiveness preliminary contamination (health-care personnel handwash only).

(v) Preoperative skin preparation effectiveness (patient preoperative skin preparation only).

(vi) Procedure for determining delay in wound healing (skin wound cleanser, skin wound protectant, skin antiseptic, patient preoperative skin preparation only).

(vii) Absence of contamination in wound (skin wound protectants only) would require testing to show no microorganisms except "normal flora" and no significant increase in microorganisms.

(2) The minimal concentration of the active ingredient necessary to produce the results required for the labeled claim(s) in each of the product classes, e.g. for antimicrobial soaps, the minimal concentration to produce deodorancy (1 $\log_{10}$ microbial reduction or significant inhibition of microbial species known to produce odor); for skin antiseptic, the concentration to "prevent skin infection" or "control infection", as the labeling provides.

V. Specific Protocols To Prove Safety and Effectiveness of Category III Ingredients

The Commissioner has extensively reviewed certain suggestions and recommendations of the Panel, as well as comments on the Panel's report, in developing specific protocols. Some of these comments and protocols follows:

A. Determination of Qualitative and Quantitative Estimation of Skin Flora (Other Than on the Hands)

1. *Skin stripping technique.* Of the techniques which have been developed, a reliable procedure for the determination of qualitative changes in the microbial skin flora consists of skin stripping of microorganisms using cellophane tape. The skin can be stripped in consecutive layers, followed by culturing and identification of organisms removed by consecutive strippings. This method can also be used to remove layers of epidermial cells to expose the glistening layer for creation of a "standard" wound for testing effectiveness of "first-aid" product classes.

2. *Cup scrubbing technique.* Cup-scrubbing technique procedures utilize a scrubbing solution placed in a cup that is attached to the skin. Some means of agitation of the liquid for more efficient removal is used.

In actual practice, the volar aspect of the forearm and the small of the back have been selected as areas for study of the flora because of ease of sampling and greater uniformity in type of flora. Individuals with a high microbial skin count should be selected as subjects for studies in which there is to be a determination of change in the number of microorganisms in any given area of the body surface. Such individuals will probably show changes in various elements of the flora more easily than those with a lower number of organisms in their normal microbial flora or in those who lack certain types of organisms.

The Commissioner is fully aware of the difficulties involved in the examination and identification of microorganisms living on the human skin. He would welcome the development of new sampling techniques and media especially selective for cutaneous microbial strains. Elaboration and improvement of the methods currently used in investigation of cutaneous ecology is desirable.

B. Effectiveness Testing of Surgical Hand Scrub (Glove Juice Test)

The Commissioner concludes that the following test must be performed to support the effectiveness of a product labeled as a surgical hand scrub:

1. *Criteria for subject selection.* a. Mixed male and female. Race should be recorded.

b. Adults.

c. Subjects will vary greatly in the number of microorganisms carried on the skin. Subjects with a high hand count as measured by sampling with the glove juice procedure should be used for the test. Counts should be in the range from 1.5×10^6 to 4×10^6 per hand.

d. Medication. Subjects receiving antibiotics or taking oral contraceptives should be excluded from the test.

e. Thirty subjects per test.

2. *Pretest period (2 weeks).* The subjects for this test should not use any products containing antimicrobials for at least 2 weeks prior to the test. This restriction includes antimicrobial antiperspirants and deodorants, shampoos, creams, lotions, soaps, or powders. Subjects receiving antibiotic therapy or taking oral contraceptives should be disqualified.

Subjects should be issued rubber gloves to be worn during their daily routine when they come in contact with detergents, acids, bases, or solvents.

3. *Gloves for test.* Gloves should be washed with sterile distilled water before use, and they should be applied wet. Gloves that are prepowdered should be carefully washed free of powder, as many of these powders contain antimicrobials.

4. *Baseline period and sampling.* The baseline period should be 1 week following the 2 weeks of the pretest period. The baseline count should begin on day one of the baseline period. The initial count is a screen to determine eligibility. The day-one count is also one count to be included for the mean baseline count. The counting procedure should be performed on day seven and also on either day three or five for a total of three estimations of the baseline count.

The baseline counts should be performed using exactly the same sampling and recovery techniques used for the test products under the testing procedure. This information will also be used to provide evidence to assess the assumption that the right and left hand gave comparable results.

Both hands should be sampled for the baseline count. Subjects should not wash prior to the counting procedure on the day of the test. This should not be construed as a 24-hour pretest ban on washing. If the test is to be run in the morning, subjects should not wash after retiring to bed on the previous night.

Baseline procedure is as follows: Hands and ⅔ of the forearm are washed for 30 seconds with Camay soap and sterile distilled water at 35° to 40° C. The excess water is shaken from the hands and the gloves are donned with the hands wet. Sampling solution (*Sampling Solution:* Triton X–100—0.1 percent in 0.075 molar phosphate buffer at a pH of 7.9) is added to the gloves (volume of sampling solution should remain constant for all tests). The glove is held closed at the wrist by the subject while an attendant massages the hand for 1 minute. A measured volume is withdrawn for the count.

5. *Scrubbing procedure.* The scrubbing procedure should be exactly as directed on the label of the product being tested, including the use of nail cleaner and/or a brush, if indicated. The hand and ⅔ of the forearm should be scrubbed.

6. *Sampling technique and times.* After the scrub is performed, loose-fitting surgeon's or examining gloves are donned. Leave the hands wet by shaking off excess water when the gloves are donned. Immediately, the designated control hand is sampled for the 1-minute count as follows: Sampling solution containing buffer and surfactant is added to the glove, the hand is massaged for 1 minute, and a measured sample removed for plating. The volume of the sampling solution added to the glove should be kept constant for all tests. The fluid should be shaken vigorously prior to dilution or culturing. If diluent is used, neutralizer should be added to dilution blanks.

The glove is to remain on the other hand for the duration of the time of the test. It is suggested that at least 1, 2, 3, 4, 5, and 6 hours post scrub should be tested.

The times for which a glove remains on one of the hands after scrub should be allocated by random selection among the subjects in groups of five. This procedure is performed on day one and day two of the test period. The procedure should be repeated on day five after scrubbing with the product according to directions two additional times on day two and three times per day on day three and day four at 1-hour intervals. One scrub should be performed on day five and the gloves allowed to remain on the left hand for 1, 2, 3, 4, 5, or 6 hours.

The number of subjects used for the test should be 30, with randomization into six groups (n=five per group) corresponding to 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, and 6 hours. The allocation of subjects to groups remains constant after initial randomization.

7. *Recovery media.* A medium containing a neutralizer specific for the antimicrobial being tested should be used. Media that have been used in the past include: Letheen and Trypticase Soy Agar with Tween 80 and serum or lecithin added.

The neutralizing system used for antimicrobial agents should be tested, and the data from the tests submitted, to show that the system is adequate. The neutralizer should not be toxic to cells and must be effective in neutralizing the specific chemical.

The cultures should be incubated at 30±2° C for 48 to 72 hours. If culturing for specific organisms, such as fungi or anaerobes, is undertaken, appropriate culturing procedures should be instituted.

Duplicate plates have been routinely used for plating in the past. Because of the inherent variability in counts and the presence of clumps of cells from skin sampling, at least triplicate plating should be used. A larger number may be required, depending on the variability. The counts should be reported as count per hand.

There are variations of this procedure in use. For instance, instead of sampling directly from the glove, the glove is removed, turned inside out into strippling fluid, and the hand rinsed with sampling solution as well. The sampling fluid consists of potassium phosphate (monobasic) 0.4 gm, sodium phosphate (dibasic) 10.1 gm, triton X–100 1.8 gm, and enough distilled water to make 1 liter. (Final pH=7.8). If variations of this test are to be used, the protocol should be checked with Food and Drug Administration personnel first.

8. *Data handling, design, and statistical aspects.* It is assumed that there are no right versus left hand differences in microbial count. It is known that microbial handedness (a difference in count between hands) exists; however, there is apparently no relationship to whether the subject is left- or right-handed. The possible difference in count should be compensated for with the initial random allocation of subjects.

This should be tested using the baseline count to validate assumptions about the influence of handedness. It is necessary, therefore, to keep data for the left and right hand distinct.

The assignment of hands is as follows: Right hand at 1 minute for determination of initial reduction from baseline (right hand baseline) on all subject (30 subjects).

Left hand glove remains on hand for measurement of extended time period (1 to 6 hours) as discussed under sampling technique and times (section V. B. 6. above).

The objective of the design is to test as follows: a. Test the $\log_{10}$ reduction from baseline 1 minute after scrubbing with fast-acting broad spectrum antimicrobials.

b. Test the initial $\log_{10}$ reduction from baseline 1 minute after scrubbing with a substantive antimocrobial.

c. Test the $\log_{10}$ reduction from baseline 1 minute after scrubbing following 3 days with three consecutive scrubs per day performed at 1-hour intervals.

9. *A test of the assumption.* A test of the assumption that the agent produces a given $\log_{10}$ reduction, such as 1-$\log_{10}$, 2-$\log_{10}$, or 3-$\log_{10}$, should be made using the data from the 1-minute result from the right hand compared to the average baseline (right hand baseline). A method like a paired t-test could be used.

10. *Left hand comparison.* Left hand at a time designated by random assignment to one of six time periods (five subjects in each of six groups) should be compared to left hand baseline.

The objective here is to characterize the trend (in microbial growth) with time up to 6 hours. It is desirable that the count, over 6 hours, with fast-acting, broad-spectrum antimicrobials not exceed the baseline. It is expected that the count will not exceed baseline in 6 hours in the testing of substantive antimicrobials.

The analyses should be performed first on each replication. There is replication of the entire test on day two and on day five after three consecutive washes at hourly intervals on day three, day four, and day five. Use the original group assignments of subjects observed for the same time periods as determined by random allocation.

Tests of trends may be done using either an orthogonal procedure or some suitable regression method. A combined analysis using the results of the three replications is possible using an appropriate analysis of variance technique. For example, an analysis of variance on the total set of experimental results using the model described on page 519 of *Statistical Principles in Experimental Design* (B. J. Winer, McGraw-Hill Book Co., 1961) where hours correspond to factor A and replications correspond to factor B. Baseline could be introduced as a covariant. Tests of trends using the orthogonal procedures should be employed.

The comments on the use of multiple plates in the culturing procedures and on the evaluation of specific neutralizers for use in the testing of antimicrobial agents apply to all in vivo testing.

C. TEST FOR ANTIMICROBIAL SOAP EFFECTIVENESS

The following test will be used to determine deodorancy effectiveness of ingredients with claims for antimicrobial soaps:

Modified Cade procedure. The Cade handwashing test was developed to standardize exposure to a given test product, usually an antimicrobial soap. The washing period was standardized in Cade's original publication. The techniques for sampling and recovery of microbiological flora have been refined over the time since the original publication. Some of these refinements are incorporated into the following discussion of the Cade test.

The data that can be derived from a Cade handwashing test are greatly expanded if a baseline level is established prior to the controlled washing with the test antimicrobial product. Thus the analyses can be expanded to give reductions from a baseline with samples from the first basin, with subsequent basins or combinations from subsequent basins.

Some adaptations of the test employ a technique for this study, which in-

volves utilizing the numbers of microorganisms determined in the first basin used for washing as a representation of the level of the transient flora. They also utilize the fourth and fifth basin to average what is considered the reduction of the resident flora achieved by the repeated handwashings. Any protocol with significantly altered procedures should be checked with FDA personnel. A proposed statistical analysis and interpretation of the data should be planned as part of the protocol. Particular care should be taken that adequate neutralization of both the soap and the antimicrobial is effected in the test procedures. Adequate selective media should be utilized to enumerate both gram-positive and gram-negative organisms.

The following outline contains only those modifications deemed necessary to approximately modify the Cade handwashing procedure (Cade, A. R., "A Method for Testing Degerming Efficiency of Hexochlorophene Soaps," *Journal of the Society of Cosmetic Chemists*, 2:281–290, 1951.):

a. Baseline should be established prior to test with at least three determinations with either Cade procedures or Glove Juice procedures.

b. *Standardized handwashing.* (1) Exposure to bar handling—at least 30 seconds.

(2) Work lather on hands—at least 60 seconds.

(3) Rinse, using a standardized treatment—at least 30 seconds.

c. *Microbial enumeration.* (1) Typticase Soy Agar.

(2) Adequate neutralization in either broth or solid medium.

(3) At least triplicate samples.

(4) Millipore filter sampling of fluid as an alternative to plating.

(5) Three-day minimum incubation at 32° to 35° C.

(6) 1-liter basin to 2-liter basin sterile water without added chlorine.

d. *Wash hands plus ⅔ of forearm.*

e. *Analysis of either:* (1) First basin or;

(2) First and/or fourth and/or fifth;

(3) Reduction from baseline to first basin;

(4) Reduction from baseline to fourth and/or fifth basin.

f. *Duration of test.* At least 10 consecutive days, optimally 14 days duration.

g. *Frequency of exposure*—3 times daily. Washout period before subjects are used in another test should be established so that no substantial residual action remains. Periods from 2 weeks to 2 months have been proposed, but actual time should be established.

h. *At least 35 subjects in test with a selected high-count subject population.* If groups are split, the analysis should specify this prior to the test and be statistically acceptable.

i. *Correlation of microbial reduction on the hands is an indication of microbial population reduction.* Actual claims of deodorancy should correlate such a microbial reduction to an adequately designed and executed deodorancy test, such as a controlled sniff test.

Data Analysis. Much data derived from this study have been analyzed with analysis of variance or other procedures to determine if a significant reduction has occurred after known expousre to the test soap. A more desirable procedure for analysis is to set a null hypothesis that a given reduction, i.e., a 1-$\log_{10}$ or 2-$\log_{10}$ reduction, has taken place and to then test that hypothesis. Determination of a statistically significant reduction alone when dealing with microbial count is a naive approach since significance can be achieved with a small reduction. Therefore the approach described above should be used.

D. TEST FOR HEALTH CARE PERSONNEL HANDWASH EFFECTIVENESS

Since the result expected from the use of this type of product is the reduction of the transient flora acquired as a result of patient care or as a part of hospital routine, the testing should involve the artificial contamination of the hands and forearms. This procedure can be executed by dipping the hands into a liquid culture with at least 10^8 organisms per ml and/or by spreading a known aliquot of the inoculum on the hands allowing 1 minute before proceeding. The artificial contamination of the hands may also be produced by handling heavily contaminated materials to simulate actual practice.

The product under test should be used according to the directions on the label. Since these products are designed to be used with multiple replication, the effectiveness testing procedure of hand contamination and washing followed by evaluation of the count of the contaminating organisms should be done at least 25 times in succession. A minimum of 5 minutes should be allowed between repeats. Evaluation of the count on the hands can be done approximately every 5 washes. The millipore filter is a well-established procedure for isolation of microorganisms from the wash water. Either the procedure recommended by the Panel or the millipore filter technique with the specifications described in the testing guidelines for the testing of health-care personnel handwashing products may be used.

In order to reliably carry out this test, a marker strain of a microorganism should be selected for use that is not part of the normal flora and that may be easily identified on culture plates. Two organisms frequently selected for this purpose are *Serratia marcescens* (pigmented strain) and *Bacillus subtilis* var. *niger* (strain globigii), Detrich isolate—American Type Culture Collection (ATCC) 9372.

E. EFFECTIVENESS OF A PATIENT PREOPERATIVE SKIN PREPARATION

The in vivo effectiveness testing procedures should utilize the skin sampling procedures set forth above (see test for antimicrobial soap effectiveness). Since any given area of skin surface can be tested, the control area can be the same location on the other half of the same subject (bilateral paired comparison).

Since the definition states that rapid activity is required, the time for testing activity should be 30-minutes maximum.

The baseline count on the control area matching the test area should be established using cup-scrubbing, tape-stripping techniques or other appropriate sampling techniques set forth above (see test for antimicrobial soap effectiveness). The same procedure should be used for skin area treated with the active product. The test must be done using an adequate population and with sampling from skin areas on various parts of the body and certainly including the genital areas.

It is essential that the sample from the skin be properly neutralized to inactivate active chemicals carried over from the skin. The neutralizer used must be tested for toxicity to cells and for effectiveness as a neutralizer. A minimum of three-log reduction will be required to establish effectiveness for a product labeled as a preoperative skin preparation.

F. EFFECTIVENESS OF A SKIN WOUND CLEANSER

Inherent in the definition is a demonstration of the product's ability to assist in the cleansing and removal of foreign material while causing no delay in wound healing.

The Commissioner recognizes that the testing of delay in wound healing, particularly in human subjects, is difficult. There is a need for the development of procedures to determine whether topical products applied to minor skin wounds would delay healing in human subjects. Until adequate human testing procedures are available, data from animal models will be required to support safety of a product to be labeled as a skin wound cleanser.

1. *Animal test for delay in wound healing.* The Commissioner concludes that the following animal test will evaluate and compare the skin wound healing delay effects of skin wound cleansers or bar soap with and without antimicrobials as well as for skin wound protectants and skin antiseptics:

a. The subjects should consist of 12 young adult male New Zealand rabbits. Both antimicrobial-treated and antimicrobial-untreated control animals should be used.

b. The back of the rabbit should be shaved so that approximately 20 percent of the total body surface area is shaved.

c. Make a wound by dermal incision in the shaved area 24 hours after clipping. A sterile technique must be followed in making the dermal incision. Disinfect the area with 70 percent isopropyl alcohol solution. Using a scalpel, six 1-inch long freehand incisions (approximately 0.5 to 1 mm deep) should be made through the dorsal skin, three on each side of the midline. These incisions should be full thickness wounds. One-half of the wounds (three incisions) should be sutured. Treatments should begin within 1 hour after wound inducement. The three treatment conditions should be soap solution with antimicrobial, soap solution without antimicrobial, and no treatment. Soap solutions should be prepared daily in tap water immediately before use. Each set of two incisions (1 sutured and 1 nonsutured

wound) should be subject to one of the treatments. One ml of soap solution (5 percent) should be gently applied for 1 to 2 minutes daily for 14 consecutive days. These daily applications should be 6 hours apart. The applied material should be allowed to dry. After the initial application, each incision should be rinsed with tap water immediately prior to subsequent treatments and gently dried. The animals should wear collars throughout the study to prevent oral ingestion of test material.

d. To evaluate the test the following parameters should be utilized: Body weight should be determined for each rabbit on days 0, 7, and 14; wound-healing progress and general conditions should be observed and described daily. This is to be supplemented by color photographs; two animals each should be sacrificed on days 1, 3, 5, 7, 10, and 14 by air injection. Wound sections should be evaluated and compared microscopically.

2. *Human test for assessment of wound repair by use of hygrometry.* The Commissioner concludes that the following test will evaluate and compare the skin wound-healing delay effects of skin wound cleansers or bar soaps with and without antimicrobials, as well as those of skin wound protectants and skin antiseptics:

a. *Insensible water loss.* The reduction of insensible water loss that occurs during the healing of adhesive tape-stripped wounds has been widely reported in the literature. The insensible water loss that is measured is often referred to as transepidermal water loss (TWL). Because of the great difference in TWL values between damaged and intact skin (50- to 100-fold), the return to normal water loss can be easily measured. This nondestructive technique allows one to follow the repair process by measuring an important physiological skin function, the ability of the body to limit loss of water to its environment. The adhesive tape-stripped wound is fairly representative of mild abrasion-type wounds for which OTC "first-aid" products are recommended. It represents a high surface area wound involving only epidermal repair, provided further physical or chemical trauma is not incurred.

b. *Method.* Strips of an industrial adhesive tape are faced to silicone release paper and cut to 1" x 1" segments for sequential stripping of the horny layer. A stripping tape is placed on the surface to be stripped and outlined at the corners with a ballpoint pen to define the area. The tapes are applied, pressed down firmly, and removed sequentially until a smooth, even, glistening surface is achieved. This usually requires 20 to 30 strips, but varies widely with the subjects used.

Adhesive tape-stripped wounds (1" x 1") are made on the upper backs of six volunteer subjects. Initial TWL values for the stripped areas are determined using an air flow hygrometry system as follows

c. *Airflow hygrometry system.* The system essentially involves the passing of dehumidified air over a 4 sq cm area of skin surface. Inflowing commercially dried air is first pressurized to maintain a constant flow, and then passed through a freeze trap at −80° C. This process reduces the probability of the "dried" air containing traces of water. The air is then passed into a heat exchanger, a radiator, and a fan to bring it to room temperature. Before the air reaches the skin, its humidity is recorded. This value is calibrated to "zero." After the air leaves the skin surface area its humidity and temperature are again monitored. The change in water content of the air after passing over the skin is determined and is equal to the TWL value.

Further information on technology and evaluation of this test (Baker, H. and A. Kligman, "Measurement of Transepidermal Water Loss by Electrical Hygrometry," *Archives of Dematology*, 96:441–452, 1967) is on file and available through the office of the Hearing Clerk (HFC–20), Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, Md. 20857.

d. *Treatment of wounds.* After initial TWL readings are taken, the wounds are treated with the various test materials. An untreated control wound is always included on each subject. The wounds are treated twice daily for 4 days. Transepidermal water loss readings are taken on all wounds on days 2 and 4 following wounding.

e. *Evaluating the data.* The transepidermal water loss values are converted to "percent damage" values according to the formula:

$$\text{Percent damage} = \frac{x}{y} \times 100$$

x = TWL values for days 2 or 4

y = TWL values for day 0

The "percent damage" figures are analyzed statistically to compare the healing rates of treated wounds with the untreated control wounds.

G. *Effectiveness Testing Of A Skin Wound Protectant.*—1. *Demonstration of the ability of a skin wound protectant to act as a barrier against further contamination with microorganisms.* a. A skin wound protectant must act as a physical barrier. The testing of barrier materials can be done with a model system and fluorescent particle challenge to the system with subsequent detection of the challenge particles on the other side of the barrier.

b. In another method acceptable to the Commissioner, the product is placed onto an area on the surface of each of six agar plates that have been prepared for use in the Andersen Air Sampler. After the Sampler has been assembled, an aerosol of bacteria is directed into the air intake opening. The aerosol is drawn through the apparatus at the standard rate of 1 cubic foot per minute. The particles drawn through the holes in the perforated metal plate in each stage of the Sampler are impinged on the agar plates beneath After the agar plates have been incubated, they are examined The bacterial colonies will conform to the pattern of the holes in the metal plates except those on areas that have been protected by an effective product

2. *Determination that a skin wound protectant does not favor the growth of microorganisms.* The second aspect of this definition to be tested is the lack of promotion of the growth of microorganisms.

a. Areas on the ventral surface of the forearms of human subjects are stripped to the glistening layer. The epidermal cells are removed by successive applications of cellophane tape to the same area One site on each arm is treated with an amount of the test preparation sufficient to cover the wound. The treated site and an untreated site on one arm are covered with an occlusive patch Commercially available Saran Wrap secured onto the area with adhesive tape is a satisfactory occlusive dressing. Comparable sites on the other arm are left air-exposed The air-expose area is treated 3 times daily. The occluded area is treated once a day.

b. Treated and control areas are sampled daily for 5 days to determine the number of bacteria present.

c. The procedure is as follows. A sterile polycarbonate cylinder 28 mm in diameter is centered on the test site A 1.5-ml aliquot of sterile physiological saline is pipetted into the cylinder, which is held firmly against the skin The skin is scraped with the tip of the pipette for 30 seconds. One ml of the resulting suspension is then removed to a tube containing 9 ml of diluent. Aliquots from this tube and from serial dilutions made from it are plated in an appropriate agar culture medium. After 48 hours aerobic incubation the colonies on the plates are counted, and the numbers of microorganisms recovered from the skin sites are calculated.

d. Evaluation. This procedure is used for accurate sampling of cutaneous microflora. This method utilizes a buffered nonionic detergent to remove all bacteria from the skin and disperse these microorganisms so the colony counts reflect single bacterial cells rather than aggregates.

Further information on evaluation of this test (Williamson, P. and A M Kligman, "A New Method for the Quantitative Investigation of Cutaneous Bacteria," *Journal of Investigative Dermatology*, 45:498–503, 1965) is on file and available through the office of the Hearing Clerk (HFC–20), Food and Drug Administration, Rm 4–65, 5600 Fishers Lane, Rockville, Md 20857.

VI. Preservative Levels of Active Ingredients

The active antimicrobial ingredients reviewed by the Panel can be formulated in topical products at various concentrations. The minimal concentration required for effectiveness as an active ingredient will be established by in vitro and in vivo efficacy testing as will the range of concentrations that can be safely used. The Commissioner recog-

nizes that many of these antimicrobial ingredients might also be added to products at much lower concentrations to prevent spoilage or growth of microorganisms, inadvertently added, introduced as a result of customer use. Many of the antimicrobials reviewed are primarily active against gram-positive microorganisms and would not generally be considered good candidates for use as preservatives. However, some of these may be considered for use of a preservative system.

Effectiveness levels for antimicrobials as preservatives can be determined by use of the antimicrobial preservatives effectiveness test of the USP XIX (p. 587) with the addition of a rechallenge procedure and stressing with an "organic load" or use of the Cosmetic Toiletry and Fragrance Association preventive tests published in 1970, with the addition of specific organisms to be tested and interpretive criteria. The specifics of these additions to the USP and CTFA tests are set forth in § 333.65 below.

Such data do not have to be submitted to the agency, but must be available upon request for inspection.

The Commissioner has reviewed the potential environmental impact of the proposed regulation and has concluded that the proposed action will not significantly affect the quality of the human environment and that an environmental impact statement is not required. The Commissioner has also considered the economic impact of the proposed regulation and no major economic impact has been found, as defined in Executive Order 11821 (as amended by Executive Order 11949) and OMB Circular A-107, and guidelines issued by the Department of Health, Education, and Welfare. Copies of the environmental impact analysis report (or statement of exemption) and environmental and economic impact assessments are on file with the Hearing Clerk, Food and Drug Administration.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)) and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243, as amended (5 U.S.C. 553, 554, 702, 703, 704)) and under authority delegated to him (21 CFR 5.1) the Commissioner of Food and Drugs is issuing as a tentative final order new Part 333 to read as follows:

PART 333—TOPICAL ANTIMICROBIAL PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Sec.
333.1 Scope.
333.3 Definitions.

Subpart B—Active Ingredients

333.20 Antimicrobial soap. [Reserved]
333.30 Patient preoperative skin preparation.
333.40 Skin wound cleanser.
333.45 Skin wound protectant. [Reserved]
333.50 Surgical hand scrub. [Reserved]

Subpart C—Testing Procedures

Sec.
333.65 Preservative testing.

Subpart D—Labeling

333.80 Antimicrobial soap.
333.85 Health-care personnel handwash.
333.87 Patient preoperative skin preparation.
333.90 Skin antiseptic.
333.92 Skin wound cleanser.
333.93 Skin wound protectant.
333.97 Surgical hand scrub.
333.99 Professional labeling.

AUTHORITY: Secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371); (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—General Provisions

§ 333.1 Scope.

An over-the-counter antimicrobial product in a form suitable for topical use is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in § 330.1 of this chapter.

§ 333.3 Definitions.

For topical preparations when applied at acceptable use concentrations as used in this part:

(a) *Antimicrobial (active) ingredient.* A compound or substance that kills microorganisms or prevents or inhibits their growth and reproduction and contributes to the claimed effects of the product in which it is included.

(b) *Antimicrobial preservative (inactive) ingredient.* A compound or substance that kills microorganisms or prevents or inhibits their growth and reproduction and is included in a product formulation only at a concentration sufficient to prevent spoilage or prevent growth of inadvertently added microorganisms, but does not contribute to the claimed effects of the product in which it is included.

(c) *Antimicrobial soap.* A soap containing an active ingredient with both in vitro and in vivo activity against skin microorganisms.

(d) *Health-care personnel handwash.* A nonirritating antimicrobial-containing preparation designed for frequent use; it reduces the number of transient microorganisms on intact skin to an initial baseline level after adequate washing, rinsing, and drying; and it is broad-spectrum, fast-acting, and, if possible, persistent.

(e) *Patient preoperative skin preparation.* A fast-acting broad-spectrum antimicrobial-containing preparation that significantly reduces the number of microorganisms on intact skin.

(f) *Skin antiseptic.* A nonirritating, antimicrobial-containing preparation that prevents overt skin infection.

(g) *Skin wound cleanser.* A nonirritating, liquid preparation (or product to be used with water) that assists in the removal of foreign material from small superficial wounds, does not delay wound healing, and that may contain an antimicrobial ingredient.

(h) *Skin wound protectant.* A nonirritating antimicrobial-containing preparation applied to small cleansed wounds; it provides a protective physical barrier and a chemical (antimicrobial) barrier that neither delays healing nor favors the growth of microorganisms.

(i) *Surgical hand scrub.* A nonirritating antimicrobial-containing preparation that significantly reduces the number of microorganisms on the intact skin. A surgical hand scrub should be broad-spectrum, fast-acting, and persistent.

(j) *Use concentration.* The dilution recommended for use as distinguished from marketed concentrates.

Subpart B—Active Ingredients

§ 330.20 Antimicrobial soap. [Reserved]

§ 333.30 Patient preoperative skin preparation.

The active ingredient of the product consists of any of the following, within the maximum dosage limit established:

(a) *Iodine tincture.* Topical dosage is for use as a solution or tincture containing not less than 1.8 gm and not more than 2.2 gm of iodine (I), and not less than 2.1 gm and not more than 2.6 gm of sodium iodide (NaI) in each 100 ml of purified water U.S.P. or 44 to 50 percent ethyl alcohol (or an appropriate denatured alcohol).

(b) [Reserved]

§ 333.40 Skin wound cleanser.

The active ingredient of the product consists of any of the following, within the potency (or concentration) established:

(a) *Quaternary ammonium-containing active ingredients.* Topical dosage for use of quaternary ammonium compounds (as benzalkonium chloride, benzethonium chloride, and methylbenzethonium chloride) is limited to a use concentration not greater than 1/750 in water. All preservative systems included in any such product formulation shall be tested according to the procedure identified in § 333.65.

(b) *Hexylresorcinol.* Topical dosage is limited to a use concentration not greater than 1/1000.

(c) *Poloxamer 188.* Topical dosage for poloxamer 188 is limited to an aqueous solution of 20 to 40 percent use concentration. The solution shall contain not less than 85 percent nor more than 100 percent of the labeled amount of poloxamer 188. All preservative systems included in any such product formulation shall be tested according to the procedure identified in § 333.65.

§ 333.45 Skin wound protectant. [Reserved]

§ 333.50 Surgical hand scrub. [Reserved]

Subpart C—Testing Procedures

§ 333.65 Preservative testing.

(a) *Determination of effective preservative concentration.* All antimicrobial ingredients used singly or as part of a preservative system for use in a topical

product identified in § 333.3(c) through (i) shall be tested by the manufacturer to establish the minimal effective preservative concentration for every product formulation by one of the following two methods:

(1) Determine the minimal effective preservative concentration according to the procedures described in the *United States Pharmacopeia* (USP) XIX (page 587) (antimicrobial preservatives effectiveness test) with the addition of a rechallenge procedure and stressing with "organic load." The preserved formulation should be tested by adding a challenge of cells (final concentration 1×10^6/milliliter) in the presence of the organic load described below. The microbial challenge should be in contact with the preserved formulation containing the organic load for a period of 15 minutes before inoculation into the preserved formulation. Then the first sample can be taken either immediately or 12 hours after inoculation. After the initial challenge, the rechallenge level should be 1×10^5 cells/milliliter. The test culture is incubated for the time specified in the USP test (2 weeks), and then the same tube is reinoculated with the rechallenge cells and again incubated for 2 weeks. The organic load consists of heat-killed yeast cells and inactivated horse or bovine serum. The yeast culture must be quantitated first and then heated to kill the cells. Then 10^6 yeast cells (*Saccharomyces cerevisiae*) per milliliter of preserved formulation should be added as the particulate organic load. The yeast cells should be added to horse or bovine serum (inactivated at 55° C for 30 minutes). Whole bovine serum should be used as the protein organic load. The results of the rechallenge test should be the same as those described in the USP test for the original challenge.

(2) The minimal effective preservative concentration of these ingredients may also be determined according to the procedures of the *Cosmetic, Toiletry and Fragrance Association Preservative Test*, with the addition of specific organisms to be used as a challenge in the test as well as the interpretive criteria described below. This test was published in the *Toilet Goods Association, Cosmetic Journal*, 2(1): 20–23, 1970, and is also available in the office of the Hearing Clerk (HFC–20), Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857. Use cultures of the following microorganisms: *Candida albicans* (ATCC No. 10231), *Aspergillus niger* (ATCC No. 16404), *Escherichia coli* (ATCC No. 8739), *Pseudomonas aeruginosa* (ATCC No. 9027), and *Staphylococcus aureus* (ATCC No. 6538). Mixed culture inoculation should not be used. Other microorganisms, in addition to those listed, may be included in the test, particularly if it appears likely that such microorganisms may represent resistant contaminants likely to be introduced during manufacture or use of the article or that such organisms may constitute a risk to the user of the final product formulation.

(b) *Preservative effectiveness.* The preservative should not allow growth of the challenge organisms in the preserved formulation. The preservative is therefore effective in the product if:

(1) The concentrations of viable bacteria are reduced to not more than 0.1 pecrent of the initial concentration by the 14th day;

(2) The concentrations of viable yeasts and molds remain at or below the initial concentrations during the first 14 days; and

(3) The concentration of each test microorganism remains at or below these designated levels during the remainder of the 28-day test period. The preservative is not effective if, after several days, repeated isolation of the microorganisms contained in the initial inoculum occurs.

(c) *Test data retention.* The resulting data from testing for every product formulation shall be available for inspection by the Food and Drug Administration.

Subpart D—Labeling

§ 333.80 Antimicrobial soap.

(a) *Statement of identity.* The labeling of the product shall contain the established name of the drug, if any, and shall identify the product as either an "antimicrobial soap" or "antibacterial soap".

(b) *Indications.* (1) *Required statements.* The labeling of the product shall contain a statement of the indications under the heading "Indications" that shall be limited to one or more of the following phrases: "Antimicrobial soap", "antibacterial soap", "antibacterial".

(2) *Other allowable statements.* The labeling may also contain the phrases "reduces odor" and "deodorant soap"; provided such phrases are neither placed in direct conjunction with information required to appear in the labeling nor occupy labeling space with greater prominence or conspicuousness than the required information.

(c) *Warnings.* The warning required by § 330.1(g) of this chapter is not required for an antimicrobial bar soap. However, the labeling of antimicrobial bar soap shall contain the following warning under the heading "Warnings": "Do not use this product on infants under 6 months of age".

(d) *Directions.* None applicable due to customary conditions of use.

§ 333.85 Health-care personnel handwash.

(a) *Statement of identity.* The labeling of the product shall contain the established name of the drug, if any, and shall identify the product as a "health-care personnel handwash".

(b) *Indications.* (1) *Required statements.* The labeling of the product shall contain a statement of the indications under the heading "Indications" that shall be limited to one or more of the following phrases: "decreases bacteria on the skin", "reduces risk and/or chance of cross-infection".

(2) *Other allowable statements.* The labeling may also contain any of the following phrases: "recommended for repeated use", "contains antibacterial ingredient", "contains antimicrobial ingredient", "fast-acting" (if applicable), and "broad-spectrum"; provided such phrases are neither placed in direct conjunction with information required to appear in the labeling nor occupy labeling space with greater prominence or conspicuousness than the required information.

(c) *Warnings.* The labeling of the product shall contain the following warning, under the heading "Warnings": "For external use only".

(d) *Directions.* The labeling of the product shall contain the following statement, under the heading "Directions": "Wet skin and spread a small amount on hands and forearms. Scrub well and rinse thoroughly after washing".

§ 333.87 Patient preoperative skin preparation.

(a) *Statement of identity.* The labeling of the product shall contain the established name of the drug, if any, and shall identify the product as a "patient preoperative skin preparation".

(b) *Indications.* (1) *Required statements.* The labeling of the product shall contain a statement of the indications under the heading "Indications" that shall be limited to one or more of the following phrases: "Kills microorganisms", "reduces the number of microorganisms in the treated area", "antibacterial", "antimicrobial".

(2) *Other allowable statements.* The labeling may also contain the phrases "broad-spectrum" and "fast-acting" (if applicable); provided such phrases are neither placed in direct conjunction with information required to appear in the labeling nor occupy labeling space with greater prominence or conspicuousness than the required information.

(c) *Warnings.* The labeling of the product shall contain the following warnings under the heading "Warnings":

(1) "For external use only".

(2) For products containing iodine tincture: "Do not apply this product with a tight bandage, as a burn may result".

(d) *Directions.* The labeling of the product shall contain the following statement under the heading "Directions" for products containing iodine tincture: "Apply to (paint) the operative site prior to surgery and remove immediately upon drying after application with 70 percent alcohol, or use as directed by a physician".

§ 333.90 Skin antiseptic.

(a) *Statement of identity.* The labeling of the product shall contain the established name of the drug, if any, and shall identify the product as a "skin antiseptic".

(b) *Indications.* (1) *Required statements.* The labeling of the product shall contain a statement of the indications under the heading "Indications" that shall be limited to one or more of the following phrases: "Prevents skin infection", "controls infection", "degerming", "kills germs", "bacteriostatic" (if applicable) "bactericidal" (if applicable), "reduces the risk of infection and cross-

infection", "microbiocidal", "first-aid product", "contains antimicrobial ingredient(s)", "contains antibacterial ingredient(s)".

(2) *Other allowable statements.* The labeling may also contain the phrase "nonirritating"; provided such phrase is neither placed in direct conjunction with information required to appear in the labeling nor occupies labeling space with greater prominence or conspicuousness than the required information.

(c) *Warnings.* The labeling of the product shall contain the following warnings under the heading "Warnings":

(1) "For external use only".

(2) "This product is not for use on wild or domestic animal bites. If you have an animal bite, consult your physician immediately".

(3) "Do not use this product for more than 10 days. If the infection worsens or persists, see your physician".

(d) *Directions.* The labeling of the product shall contain the following statement under the heading "Directions": "Apply to affected area." The labeling shall also contain the recommended dosage for use, time interval (if any), and method by which the product shall be used to prevent overt skin infection for those particular organisms for which the product is generally recognized as safe and effective.

§ 333.92 Skin wound cleanser.

(a) *Statement of identity.* The labeling of the product shall contain the established name of the drug, if any, and shall identify the product as a "skin wound cleanser".

(b) *Indications.* (1) *Required statements.* The labeling of the product shall contain a statement of the indications under the heading "Indications" that shall be limited to one or more of the following phrases: "To clean superficial wounds," "for washing small superficial wounds," "aids in removal of foreign material such as dirt and debris," "first-aid product."

(2) *Other allowable statements.* The labeling may also contain any of the following phrases: "Nonirritating," "does not delay wound healing," "contains antibacterial ingredient" (if applicable), and "contains antimicrobial ingredient" (if applicable); provided such phrases are neither placed in direct conjunction with information required to appear in the labeling nor occupy labeling space with greater prominence or conspicuousness than the required information.

(c) *Warnings.* The labeling of the product shall contain the following warnings under the heading "Warnings":

(1) "For external use only."

(2) "This product is not for use on wild or domestic animal bites. If you have an animal bite, consult your physician immediately."

(3) "Do not use this product for more than 10 days. If condition worsens or persists, see your physician."

(4) "Do not bandage tightly."

(5) For products marketed as concentrates: *"Caution:* Use only after dilution to use concentration. May cause eye irritation or eye damage unless diluted."

(6) For concentrated products containing quaternary ammonium compounds: "Dilute with distilled water before use because acidic or hard water may render the product inactive."

(d) *Directions.* The labeling of the product shall contain the following statement under the heading "Directions": "Apply to affected area". The labeling shall also contain the recommended dosage for use and method by which the product shall be used to cleanse a small wound without further damage to the injured area.

§ 333.93 Skin wound protectant.

(a) *Statement of identity.* The labeling of the product shall contain the established name of the drug, if any, and shall identify the product as a "skin wound protectant."

(b) *Indications.* (1) *Required statements.* The labeling of the product shall contain a statement of the indications under the heading "Indications" that shall be limited to one or more of the following phrases: "Protectant," "protects wounds," "firstaid product," "first-aid for small (minor) cuts, abrasions and burns," "protectant for small (minor) cuts, abrasions, and burns," "protects against wound contamination."

(2) *Other allowable statements.* The labeling may also contain any of the following phrases: "Nonirritating," "provides a protective physical (and chemical) barrier," "does not delay wound healing," "contains antibacterial ingredient(s)" and "contains antimicrobial ingredient(s)"; provided such phrases are neither placed in direct conjunction with information required to appear in the labeling nor occupy labeling space with greater prominence or conspicuousness than the required information.

(c) *Warnings.* The labeling of the product shall contain the following warnings, under the heading "Warnings":

(1) "For external use only."

(2) "This product is not for use on wild or domestic animal bites. If you have an animal bite, consult your physician immediately."

(3) Do not use this product for more than 10 days. If the conditions worsen or persist, see your physician."

(4) *Caution:* In case of deep or puncture wounds or serious burns consult your physician."

(5) "If itching, redness, irritation, swelling or pain develops and persists for more than 1 week or increases, it may be a sign of infection or allergy. Discontinue use at once and consult your physician."

(6) "Do not use in the eyes."

(7) "Do not use on chronic skin conditions such as leg ulcers, diaper rash, or hand eczema."

(d) *Directions.* The labeling of the product shall contain the following statement under the heading "Directions": "After gentle washing with soap and water, apply a small amount directly to the affected area and cover with sterile gauze if desired. May be applied 1 to 3 times daily".

§ 333.97 Surgical hand scrub.

(a) *Statement of identity.* The labeling of the product shall contain the established name of the drug, if any, and shall identify the product as a "surgical hand scrub".

(b) *Indications.* (1) *Required statements.* The labeling of the product shall contain a statement of the indications under the heading "Indications" that shall be limited to one or more of the following phrases: "Kills microorganisms", "significantly reduces the number of microorganisms on the hands and forearms prior to surgery or patient care", "bacteriostatic", "bactericidal".

(2) *Other allowable statements.* The labeling may also contain any of the following phrases: "Nonirritating", "fast-acting" (if applicable), "broad-spectrum" (if applicable), "contains antimicrobial ingredients", and "contains antibacterial ingredient(s)" provided such phrases are neither placed in direct conjunction with information required to appear in the labeling nor occupy labeling space with greater prominence or conspicuousness than the required information.

(c) *Warnings.* The labeling of the product shall contain the following warning under the heading "Warnings": "For external use only".

(d) *Directions.* The labeling of the product shall contain the following statement under the heading "Directions": "Wet hands. Apply 5 ml (teaspoonful) or appropriate quantity to hands and forearms. Scrub thoroughly for 5 minutes or other appropriate time. Rinse and repeat". The labeling shall also contain such other directions as the product formulation and good medical practice dictate.

§ 333.99 Professional labeling.

The labeling for each type of product defined in § 333.3 (c) through (i) that is provided only to health professionals and the labeling for those products primarily used in health-care facilities shall contain, in addition to the warnings required by each monograph, the following:

(a) *"Caution:* Overuse of this and other antimicrobial products may result in an overgrowth of gram-negative organisms, particularly *Pseudomonas.* These effects could be serious in severely debilitated patients or patients at high risk such as burn victims, the elderly, or newborns".

(b) For products containing quaternary ammonium compounds: "This product is rendered inactive by hard water, acidic water, anionic compounds, soaps Tween 80 and sodium lauryl sulfate".

(c) The warning "Do not use solution with occlusive dressing" may be used instead of the warning "Do not bandage tightly" in the "Warnings" section of the labeling for a skin wound cleanser product.

Interested persons may file written objections and request an oral hearing before the Commissioner regarding this tentative order on or before February 6, 1978. Requests for an oral hearing must specify points to be covered and time requested. All objections and requests shall be submitted (in quintuplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) to the Hearing Clerk (HFC–20), Food and Drug Administration (HFC–20), room 4–65, 5600 Fishers Lane, Rockville, Md. 20857, and may be accompanied by a memorandum or brief in support thereof. Objections and requests may be seen in the above office, between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the FEDERAL REGISTER.

The Food and Drug Administration has determined that this document does not contain a major proposal requiring preparation of an economic impact statement under Executive Order 11821 (as amended by Executive Order 11949) and OMB Circular A–107. A copy of the economic impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Dated: December 23, 1977.

DONALD KENNEDY,
Commissioner of Food and Drugs.

[FR Doc.78–3 Filed 1–5–78;8:45 am]